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(54) **Amphoteric compositions and polymeric forms of alpha hydroxyacids, and their therapeutic use.**

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Description

This invention relates generally to therapeutic treatment as well as preventive measures for cosmetic conditions and dermatologic disorders by topical administration of amphoteric compositions or polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds. We initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that amphoteric compositions and polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds on topical administration are therapeutically effective for various cosmetic conditions and dermatologic disorders.

In our prior U.S. Patent No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of certain alpha hydroxyacids, alpha ketoacids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Patent No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Patent No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed the use of alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dry skin. In our recent U.S. Patent No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxyacids, alpha ketoacids and their derivatives, could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Patent No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus, warts and herpes.

In EP-A-0 273 202 entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed that incorporation of an alpha hydroxyacid or related compound can substantially enhance therapeutic actions of cosmetic and pharmaceutical agents.

There is no doubt that alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles and disturbed keratinization. However, the compositions containing these acids may irritate human skin on repeated topical applications due to lower pH of the formulations. The irritation may range from a sensation of tingling, itching and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1 M) glycolic acid has a pH of 1.9, and a composition containing 9% (1 M) lactic acid has the same pH of 1.9. These compositions of lower pH on repeated topical applications can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings resulting in adverse skin reactions, especially to some individuals with sensitive skin.

Moreover, with today's state of the art it is still very difficult to formulate a lotion, cream or ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is physically stable as a commercial product for cosmetic or pharmaceutical use.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with a metallic alkali such as sodium hydroxide or potassium hydroxide the composition becomes therapeutically ineffective. The reasons for such loss of therapeutic effects are believed to be as follows:

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or other systematic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors; (a) bioavailability of the active ingredient in the topical preparation and (b) percutaneous absorption, penetration and distribution of the active ingredient to the target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but that containing 5% sodium salicylate is not an effective product. The reason for such difference is that salicylic acid is in bioavailable form and can penetrate the

stratum corneum, but sodium salicylate is not in bioavailable form and cannot penetrate the stratum corneum of the skin.

In the case of alpha hydroxyacids, a topical preparation containing 5% glycolic acid is therapeutically effective for dry skin, but that containing 5% sodium glycollate is not effective. The same is true in case of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both glycolic acid and lactic acid are in bioavailable forms and can readily penetrate the stratum corneum, but sodium glycollate and sodium lactate are not in bioavailable forms and cannot penetrate the stratum corneum of the skin.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with ammonium hydroxide or an organic base of smaller molecule the composition still shows some therapeutic effects for certain cosmetic conditions such as dry skin, but the composition has lost most of its potency for other dermatologic disorders such as wrinkles, keratoses, age spots and skin changes associated with aging.

The present invention consists in a pharmaceutical or cosmetic composition for topical application, said composition comprising an active ingredient selected from alpha hydroxyacids, alpha ketoacids, dimeric and polymeric forms of hydroxyacids, ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid, pantoic acid, lactones derived from said acids and salts of said acids with organic bases or inorganic alkalis, in a pharmaceutically acceptable vehicle for topical application, characterized in that the composition comprises an amphoteric system consisting essentially of said active ingredient in combination with an amphoteric or pseudoamphoteric organic compound, which acts to raise the overall pH of the composition.

It has been discovered that amphoteric compositions containing the aforementioned alpha hydroxyacids, alpha ketoacids or related compounds overcome the aforementioned shortcomings and retain the therapeutic efficacies for cosmetic and conditions and dermatologic disorders. The amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

I. Amphoteric and Pseudoamphoteric Compositions

Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. The acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are amino acids, peptides, polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or capable of inducing the same function when they are incorporated into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine and stearamidopropyl dimethylamine.

There are two advantages of utilizing an amphoteric or pseudoamphoteric compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as a buffering system to control the release of alpha hydroxy or ketoacid into the skin, therefore, eliminating the skin irritation and still retaining the therapeutic efficacies.

The following are some examples. 2-Hydroxyethanoic acid (glycolic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.0 and 3.2 when arginine 0.5 M and creatinine 0.5 M respectively are incorporated into the formulations. 2-Hydroxypropanoic acid (lactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.1 and 6.9 when arginine 0.5 M and 1.0 M respectively are incorporated into the formulations. 2-Methyl 2-hydroxypropanoic acid (methyl lactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.3, 3.4 and 3.2 when 0.5 M each of arginine,

creatinine and 4-aminobutanoic acid respectively are incorporated into the formulations. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1 M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatinine 0.5 M is incorporated into the formulation.

Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base.

Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid type, (b) imidazoline and lecithin amphoteric and (c) pseudoamphoterics and miscellaneous amphoteric.

(a) Amino acid type amphoteric. Amphoteric compounds of amino acid type include all the amino acids, dipeptides, polypeptides, proteins and the like which contain at least one of the basic groups such as amino, imino, guanido, imidazolino and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic and sulfate.

Glycine is a simple amphoteric compound which contains only one amino group and one carboxylic group. Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanido group and one carboxylic group. Histidine contains one amino group, one imidazolyl group and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfinic acid contains one amino group, one carboxylic group and one sulfinic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine N,N,N-trimethyl inner salt.

Glycylglycine is a simple dipeptide which contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide which contains one free amino group, one imidazolyl group and one free carboxylic group.

The representative amphoteric compounds of amino acid type may be listed as follows: Glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline and proline.

The related amino acids include homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β -lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2-methylserine, 3-phenylserine and betaine.

Sulfur-containing amino acids include taurine, cysteinesulfinic acid, methionine sulfoxide and methionine sulfone.

The halogen-containing amino acids include 3,5-diiodotyrosine, thyroxine and monoiodotyrosine. The imino type acids include pipercolic acid, 4-aminopipercolic acid and 4-methylproline.

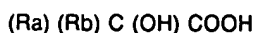
The dipeptides include for example, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β -alanyllysine, β -alanylarginine. The tripeptides include for example, glutathione, ophthalmic acid and norophthalmic acid. Short-chain polypeptides of animal, plant and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine and arginine rich proteins.

(b) Imidazoline and lecithin amphoteric. The amphoteric compounds of imidazoline derived type are commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminoethylethanolamine. These amphoteric include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include for example, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

(c) Pseudoamphoterics and miscellaneous amphoteric. Many pseudoamphoteric compounds are chemically related or derived from true amphoteric. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines such as stearamidoethyl diethylamine, stearamidoethyl diethanolamine and stearamidopropyl dimethylamine.

In accordance with the present invention, the alpha hydroxyacid, the alpha ketoacids and the related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders may be classified into three groups.

The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:



where Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The

- 5 alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.
- Typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) polycarboxylic alpha hydroxyacids. The following are representative alpha hydrox-
- 10 yacids in each subgroup.

(1) Alkyl Alpha Hydroxyacids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid)
15 (H) (H) C (OH) COOH
2. 2-Hydroxypropanoic acid (Lactic acid)
(CH₃) (H) C (OH) COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methylactic acid)
(CH₃) (CH₃) C (OH) COOH
- 20 4. 2-Hydroxybutanoic acid
(C₂H₅) (H) C (OH) COOH
5. 2-Hydroxypentanoic acid
(C₃H₇) (H) C (OH) COOH
6. 2-Hydroxyhexanoic acid
25 (C₄H₉) (H) C (OH) COOH
7. 2-Hydroxyheptanoic acid
(C₅H₁₁) (H) C (OH) COOH
8. 2-Hydroxyoctanoic acid
(C₆H₁₃) (H) C (OH) COOH
- 30 9. 2-Hydroxynonanoic acid
(C₇H₁₅) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid
(C₈H₁₇) (H) C (OH) COOH
11. 2-Hydroxyundecanoic acid
35 (C₉H₁₉) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)
(C₁₀H₂₁) (H) C (OH) COOH
13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)
(C₁₂H₂₅) (H) C (OH) COOH
- 40 14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)
(C₁₄H₂₉) (H) C (OH) COOH
15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)
(C₁₆H₃₃) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)
45 (C₁₈H₃₇) (H) C (OH) COOH

(2) Aralkyl And Aryl Alpha Hydroxyacids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)
50 (C₆H₅) (H) C (OH) COOH
2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid)
(C₆H₅) (C₆H₅) C (OH) COOH
3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)
(C₆H₅CH₂) (H) C (OH) COOH
- 55 4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid)
(C₆H₅) (CH₃) C (OH) COOH
5. 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid (4-Hydroxymandelic acid)
(HO-C₆H₄) (H) C (OH) COOH

6. 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid)
 $(\text{Cl}-\text{C}_6\text{H}_4) (\text{H}) \text{C} (\text{OH}) \text{COOH}$
7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid
 (3-Hydroxy-4-methoxymandelic acid) $(\text{HO}-\text{CH}_2\text{O}-\text{C}_6\text{H}_3) (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 5 8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid
 (4-Hydroxy-3-methoxymandelic acid)
 $(\text{HO}-\text{CH}_2\text{O}-\text{C}_6\text{H}_3) (\text{H}) \text{C} (\text{OH}) \text{COOH}$
9. 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(2'-Hydroxyphenyl) lactic acid]
 $\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 10 10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4'-Hydroxyphenyl) lactic acid]
 $\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid)
 $\text{HO}-\text{HO}-\text{C}_6\text{H}_3 (\text{H}) \text{C} (\text{OH}) \text{COOH}$

15 (3) Polyhydroxy Alpha Hydroxyacids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid)
 $(\text{HOCH}_2) (\text{H}) \text{C} (\text{OH}) \text{COOH}$
2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)
 $\text{HOCH}_2 (\text{HO})\text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 20 3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid)
 $\text{HOCH}_2 (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)
 $\text{HOCH}_2 (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 25 5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)
 $\text{HOCH}_2 (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{HO})\text{CH} (\text{H}) \text{C} (\text{OH}) \text{COOH}$

(4) Polycarboxylic Alpha Hydroxyacids

- 30 1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)
 $\text{HOOC} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)
 $\text{HOOC} \text{CH}_2 (\text{H}) \text{C} (\text{OH}) \text{COOH}$
- 35 3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)
 $\text{HOOC} (\text{HO})\text{CH} (\text{H}) \text{C} (\text{OH}) \text{COOH}$
4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)
 $\text{HOOC} \text{CH}_2 \text{C} (\text{OH})(\text{COOH}) \text{CH}_2 \text{COOH}$
5. 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid etc.)
 $\text{HOOC} (\text{CHOH})_4 \text{COOH}$
- 40

(5) Lactone Forms

The typical lactone forms are gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.

The second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the alpha carbon of the acids is in keto form. The generic structure of such alpha ketoacids may be represented as follows:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl,

lauryl, stearyl, benzyl and phenyl, etc.

The representative alpha ketoacids which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid)
5 (H) CO COOH
2. 2-Ketopropanoic acid (Pyruvic acid)
CH₃ CO COOH
4. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid)
C₆H₅ CO COOH
- 10 5. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid)
C₆H₅CH₂ CO COOH
6. 2-Ketobutanoic acid
C₂H₅ CO COOH
7. 2-Ketopentanoic acid
15 C₃H₇ CO COOH
8. 2-Ketohexanoic acid
C₄H₉ CO COOH
9. 2-Ketoheptanoic acid
C₅H₁₁ CO COOH
- 20 10. 2-Ketooctanoic acid
C₆H₁₃ CO COOH
11. 2-Ketododecanoic acid
C₁₀H₂₁ CO COOH

25 The third group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic and dermatologic conditions and disorders, is chemically related to alpha hydroxyacids or alpha ketoacids, and can be represented by their names instead of the above two generic structures. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

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II. Dimeric and Polymeric Forms of Hydroxyacids

When two or more molecules of hydroxycarboxylic acids either identical or non-identical compounds are reacted chemically to each other, dimeric or polymeric compounds will be formed. Such dimeric and 35 polymeric compounds may be classified into three groups, namely (a) acyclic ester, (b) cyclic ester and (c) miscellaneous dimer and polymer.

(a) Acyclic ester. The acyclic ester of a hydroxycarboxylic acid may be a dimer or a polymer. The dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed from 40 two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactyl lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly reacted, a different dimer is formed. For example, glycolyl lactate is formed by reacting the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid. For example, glycoly 45 glycolyl glycollate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycollate is formed from two molecules of glycolic acid and one molecule of lactic acid.

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

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wherein Ra,Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=2 or more with a 55 preferred value of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra,Rb=H in monomer unit 1, and Ra=CH₃,Rb=H in monomer unit 2 when n=2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb

may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolyl glycollate (Glycolic acid glycollate)

Ra,Rb = H in units 1 & 2, n = 2

2. Lactyl lactate (Lactic acid lactate)

Ra = CH₃, Rb = H in units 1 & 2, n = 2

3. Mandelyl mandellate

Ra = C₆H₅, Rb = H in units 1 & 2, n = 2

4. Atrolactyl atrolactate

Ra = C₆H₅, Rb = CH₃ in units 1 & 2, n = 2

5. Phenyllactyl phenyllactate

Ra = C₆H₅CH₂, Rb = H, in units 1 & 2, n = 2

6. Benzilyl benzillate

Ra,Rb = C₆H₅ in units 1 & 2, n = 2

7. Glycolyl lactate

Ra = CH₃ in unit 1, Ra = H in unit 2, Rb = H in units 1 & 2, n = 2

8. Lactyl glycollate

Ra = H in unit 1, Ra = CH₃ in unit 2, Rb = H in units 1 & 2, n = 2

9. Glycolyl glycolyl glycollate

Ra,Rb = H in units 1, 2 & 3, n = 3

10. Lactyl lactyl lactate

Ra = CH₃, Rb = H in units 1, 2 & 3, n = 3

11. Lactyl glycolyl lactate

Ra = CH₃ in units 1 & 3, Ra = H in unit 2, Ra = H in units 1, 2 & 3, n = 3

12. Glycolyl glycolyl glycolyl glycollate

Ra,Rb = H in units 1, 2, 3 & 4, n = 4

13. Lactyl lactyl lactyl lactate

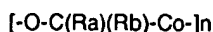
Ra = CH₃, Rb = H in units 1, 2, 3 & 4, n = 4

14. Glycolyl lactyl glycolyl lactyl glycollate

Ra = H in units 1, 3 & 5, Ra = CH₃ in units 2 & 4, Rb = H in units 1, 2, 3, 4 & 5, n = 5

15. Polyglycolic acid and polylactic acid

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:



wherein Ra,Rb = H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n = 2 or more. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, CH₃ in unit 2 and Rb is H in both units 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolide

Ra,Rb = H, n = 2

2. Lactide
Ra = CH₃, Rb = H in units 1 & 2, n = 2
3. Mandelide
Ra = C₆H₅, Rb = H in units 1 & 2, n = 2
- 5 4. Atrolactide
Ra = C₆H₅, Rb = CH₃ in units 1 & 2, n = 2
5. Phenyllactide
Ra = C₆H₅ CH₂, Rb = H in units 1 & 2, n = 2
6. Benzilide
Ra, Rb = C₆H₅ in units 1 & 2, n = 2
- 10 7. Methylactide
Ra, Rb = CH₃ in units 1 & 2, n = 2
8. Lactoglycolide
Ra = H in unit 1, Ra = CH₃ in unit 2
Rb = H in units 1 & 2, n = 2
- 15 9. Glycolactide
Ra = CH₃ in unit 1, Ra = H in unit 2
Rb = H in units 1 & 2, n = 2

(c) Miscellaneous dimer and polymer. This group includes all the dimeric and polymeric forms of hydroxycarboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethocanic acid and aleuritic acid. When a hydroxycarboxylic acid has more than one hydroxy or carboxy group in the molecule a complex polymer may be formed. Such complex polymer may consist of acyclic as well as cyclic structures.

The following hydroxycarboxylic acids have more than one hydroxy groups: glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone. These polyhydroxycarboxylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxycarboxylic acids have more than one carboxyl groups: malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid. These monohydroxypolycarboxylic acids can also form complex polymers with themselves or with other simple hydroxycarboxylic acids.

The following hydroxycarboxylic acids have more than one hydroxy and more than one carboxyl groups: tartaric acid, mucic acid and saccharic acid. These polyhydroxypolycarboxylic acids can form even more complex polymers with themselves or with other hydroxycarboxylic acids.

35 III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxyacids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; antimotion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidryskin agents; antiperspirants; anti-psoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents and other dermatologicals.

Some examples of cosmetic and pharmaceutical agents are clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate and vitamin E acetate.

IV. Specific Compositions For Skin Disorders

We have discovered that topical formulations or compositions containing specific alpha hydroxyacids or alpha ketoacids, or related compounds are therapeutically very effective for certain skin disorders without utilizing any amphoteric or pseudoamphoteric systems. The alpha hydroxyacids and the related compounds include 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

In general, the concentration of the alpha hydroxyacid, the alpha ketoacid or the related compound used in the composition is a full strength to an intermediate strength, therefore the dispensing and the application require special handling and procedures.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength (usually 95-100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength is a solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the solid compound is first dissolved in a minimal amount of vehicle or vehicle system such as water, or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, 0.5 to 3% of for example, hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose or carbomer may be incorporated into the above solution.

To prepare an intermediate strength (usually 20-50%), the alpha hydroxyacid, alpha ketoacid or related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system such as water, acetone, ethanol, propylene glycol and butane 1,3-diol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

For topical treatment of warts, keratoses, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine-caliber, commonly available artist's camel hair brush to affected lesions only and not surrounding skin. Prescribed applications have been 1 to 6 times daily for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging related skin changes topical applications have been 1 to 2 times daily.

Very often, frequency and duration of applications have been modified according to clinical responses and reactions of the lesions and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2-hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

Preparation of the Therapeutic Compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form at least one of the aforementioned amphoteric or pseudoamphoteric compounds and in combination at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10 M, the preferred concentration ranges from 0.1 to 3 M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12 M, the preferred concentration ranges from 0.2 to 5 M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are initially dissolved in a solvent such as water, ethanol and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base
 5 such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are dissolved in a
 10 mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, octyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not
 20 require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from 1 to 40%. Therapeutic compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

To prepare a combination composition in a pharmaceutically acceptable vehicle, a cosmetic or
 25 pharmaceutical agent is incorporated into any one of the above composition by dissolving or mixing the agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative. Therefore, any of the aforementioned amphoteric or pseudoamphoteric
 30 compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substituted according to the teachings of this invention in the following examples.

EXAMPLE 1

35 An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An
 40 amphoteric composition formulated from 1 M 2-hydroxyethanoic acid and 1 M L-arginine has pH 6.3. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 2

45 An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The
 50 amphoteric composition thus formulated has pH 3.3.

EXAMPLE 3

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

55 2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.1.

EXAMPLE 4

A pseudoamphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

- 5 2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.0 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

10 EXAMPLE 5

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

- 15 2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 6

- 20 An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M dipeptide of β -Ala-L-His for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and L-carnosine (β -alanyl-L-histidine) 11.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.5.

25

EXAMPLE 7

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M cycloleucine for cosmetic and dermatologic conditions may be formulated as follows.

- 30 2-Hydroxyethanoic acid 3.8 g and 1-aminocyclopentane-1-carboxylic acid (cycloleucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

35 EXAMPLE 8

A pseudoamphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.25 M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

- 40 2-Hydroxyethanoic acid 3.8 g and 1,12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 9

45

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

- 50 2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 10

- 55 An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus

formulated has pH 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has pH 6.9. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 11

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4

EXAMPLE 12

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0

EXAMPLE 13

A pseudoamphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 14

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated as pH 4.9.

EXAMPLE 15

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and glycylglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 16

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid (methyl-lactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. An amphoteric composition formulated from 1 M 2-methyl-2-hydroxypropanoic acid and 1 M L-arginine has pH 6.5. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 17

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

10 EXAMPLE 18

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and glycylglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 19

20 A pseudoamphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 20

30 An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 5.0. The composition has pH 2.2 if no amphoteric compound is incorporated.

EXAMPLE 21

40 An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

45 EXAMPLE 22

A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

50 2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

EXAMPLE 23

55 An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in

volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 24

5 An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

15 A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.7.

20 EXAMPLE 26

An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

25 2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 27

30 A pseudoamphoteric composition containing 1 M malic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.0. The composition has pH 3.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 28

40 An amphoteric composition containing 1 M tartaric acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.7 if no amphoteric compound is incorporated.

EXAMPLE 29

50 A pseudoamphoteric composition containing 1 M tartaric acid and 1 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4.

55 EXAMPLE 30

An amphoteric composition containing 1 M gluconolactone and 0.5 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. The composition has pH 5.9 when 1 M instead of 0.5 M L-arginine is incorporated into the formulation. If no amphoteric compound is incorporated
5 the pH of the composition is 1.8.

EXAMPLE 31

An amphoteric composition containing 1 M gluconolactone and 0.5 M 4-aminobutanoic acid for
10 cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 32

An amphoteric composition containing 1 M gluconolactone and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml.
20 More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1

EXAMPLE 33

A pseudoamphoteric composition containing 1 M gluconolactone and 0.5 M creatinine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Gluconolactone 17.8 g and creatinine 5.7 g are dissolved in water 60 ml and propylene glycol 10 ml. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.8 when 1 M instead of 0.5 M creatinine is
30 incorporated into the formulation.

EXAMPLE 34

A pseudoamphoteric composition containing 1 M pyruvic acid and 1 M creatinine for dermatologic and
35 cosmetic conditions may be formulated as follows.

2-Ketopropanoic acid (pyruvic acid) 8.8 g and creatinine 11.3 g are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.4.

EXAMPLE 35

An amphoteric composition containing 0.5 M benzoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzoic acid) 11.4 g and L-lysine 7.3 g are dissolved in water 40
45 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9. The composition has pH 2.7 if no amphoteric compound is incorporated.

EXAMPLE 36

An amphoteric composition containing 0.5 M benzoic acid and 0.5 M L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

Benzoic acid 11.4 g and L-histidine 7.8 g are dissolved in water 40 ml and propylene glycol 20 ml. Ethyl cellulose 2 g is added with stirring, and sufficient amount of ethanol is added to make a total volume
55 of the gel to 100 ml. The amphoteric gel composition thus formulated has pH 5.0.

EXAMPLE 37

A pseudoamphoteric composition containing 0.5 M benzoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

- 5 Benzoic acid 11.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. Sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9.

EXAMPLE 38

- 10 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05 % betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

- 2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1 % in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 39

- 20 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

- 2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1 % in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 40

- 30 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

- 2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 41

- A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.2 % 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

- 40 2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol: water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

45 EXAMPLE 42

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.05 % betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

- 50 2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 43

- 55 A pseudoamphoteric composition containing in combination 0.5 M hydroxypropanoic acid and 0.05 % clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

5

EXAMPLE 44

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.1 % triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

10 2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

15 **EXAMPLE 45**

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.2 % 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

20 2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol:water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 46

25

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% clotrimazole in a cream form for athlete's foot and other fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in water 20 ml and propylene glycol 5 ml, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 47

35 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% erythromycin in solution form for acne may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, erythromycin 2 g and creatinine 5.7 g are dissolved in water 25 ml, ethanol 40 ml and propylene glycol 15 ml. More water is then added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

40 **EXAMPLE 48**

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 1 % ketoconazole in a cream form for fungal infections may be formulated as follows.

45 2-Hydroxyethanoic acid 3.8 g, ketoconazole 1 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 49

50 A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 2% clotrimazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxypropanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

55

EXAMPLE 50

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% tetracycline in a gel form for dermatologic disorders may be formulated as follows.

5 2-Hydroxyethanoic acid 3.8 g, tetracycline 2 g, creatinine 5.7 g, xanthan gum 0.2 g, carbomer-941 1 g, propylene glycol 5 ml, ethanol 20 ml and enough amount of water are homogenized to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated for acne and oily skin has pH 4.2.

EXAMPLE 51

10

An amphoteric composition containing 0.2 M aleuritic acid and 0.1 M L-lysine in a solution form for cosmetic and dermatologic conditions may be formulated as follows.

Aleuritic acid 6.1 g and L-lysine 1.5 g are dissolved in sufficient amount of a solution from ethanol:propylene glycol 80:20 to make a total volume of 100 ml. The amphoteric composition thus
15 formulated has pH 6.4.

EXAMPLE 52

A typical composition containing a dimeric form of alpha hydroxyacid in solution for acne, dandruff, and
20 as a skin cleanser may be formulated as follows.

Glycolide powder 1.0 g is dissolved in ethanol 89 ml and propylene glycol 10 ml. The composition thus formulated has pH 4.0, and contains 1% active ingredient.

EXAMPLE 53

25

A typical composition containing a dimeric form of alpha hydroxyacid in ointment for dry skin, psoriasis, eczema, pruritus, wrinkles and other skin changes associated with aging may be formulated as follows.

Glycolide powder 2.0 g is mixed uniformly with petrolatum 66 g and mineral oil 32 g. The composition thus formulated contains 2% active ingredient.

30

EXAMPLE 54

A typical composition containing a full strength or a high concentration of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatments of warts, keratoses, acne, age spots, nail
35 infections, wrinkles and aging related skin changes may be prepared as follows.

If the alpha hydroxyacid, alpha ketoacid or closely related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a solid form at room temperature such as 2-hydroxyethanoic acid and 2-methyl 2-hydroxypropanoic acid, it is first dissolved in minimal amount of an appropriate solvent or solvent system such as
40 water or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength 2-hydroxyethanoic acid thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, methyl cellulose or hydroxyethyl cellulose 1 g may be added to the above solution.

45

EXAMPLE 55

A typical composition containing an intermediate strength of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatment of warts, keratoses, acne, nail infections, age spots, wrinkles
50 and aging related skin changes may be prepared as follows.

2-Hydroxyethanoic acid or 2-ketopropanoic acid 40 g is dissolved in ethanol 54 g and propylene glycol 6 g, and the 40% strength solution thus obtained is dispensed as 5 to 10 ml aliquots in dropper bottles.

TEST RESULTS

55

In order to determine whether amphoteric and pseudoamphoteric compositions of the instant invention were therapeutically effective for various cosmetic conditions and dermatologic disorders, a total of more than 90 volunteers and patients participated in these studies. Some participating subjects were given two

preparations; an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound, and a vehicle placebo. Others were given multiple preparations containing a known pharmaceutical agent such as a corticosteroid with or without incorporation of an amphoteric or pseudoamphoteric composition consisting of an alpha hydroxyacid or the related compound of the instant invention.

5 The amphoteric and pseudoamphoteric compositions were formulated according to the Examples described in the previous section.

1. Common dry skin.

10 Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dryness, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing an alpha hydroxyacid or the related compound in amphoteric or pseudoamphoteric composition, on the affected area of the skin. Topical application, two to three times daily, was continued for two to four weeks.

15 In all the 28 subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after several days of topical treatment. The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective when incorporated into the amphoteric or pseudoamphoteric compositions for dry skin are as follows:

20 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl-2-hydroxypropanoic acid (methylactic acid), phenyl 2-hydroxyethanoic acid (mandelic acid), phenyl 2-methyl-2-hydroxyethanoic acid (atrolactic acid), 3-phenyl-2-hydroxypropanoic acid (phenyllactic acid), diphenyl 2-hydroxyethanoic acid (benzilic acid), gluconolactone, tartaric acid, citric acid, saccharic acid, malic acid, tropic acid, glucuronic acid, galacturonic acid, gluconic acid, 3-hydroxybutanoic acid, quinic acid, ribonolactone, glucuronolactone, galactonolactone, pyruvic acid, phenylpyruvic acid and benzoylformic acid.

25 The ordinary dry skin conditions, once restored to normal appearing skin, remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound of the instant invention prevented the development of new dry skin lesions.

2. Severe dry skin.

35 In severe dry skin, the skin lesions are different from the ordinary dry skin. A main cause of severe dry skin is inherited genetic defects of the skin. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

DEGREE OF IMPROVEMENT					
	None (0)	Mild (1 +)	Moderate (2 +)	Substantial (3 +)	Complete (4 +)
45 Thickness	Highly elevated	Detectable reduction	Readily apparent reduction	Barely elevated	Normal thickness
Texture	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth

50 By means of such parameters, degrees of change in lesions can be numerically recorded and comparisons made of one treated site to another.

In order to evaluate the amphoteric and pseudoamphoteric compositions of the instant invention, a total of 6 patients having severe dry skin conditions were treated with the compositions containing an alpha hydroxyacid or the related compound.

55 Tested areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal lotions or creams were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made

three times daily and without occlusive dressings. Applications were discontinued at any time when resolutions of the lesion on the treatment area was clinically judged to be complete.

The test results of amphoteric and pseudoamphoteric compositions containing the following alpha hydroxyacids or the related compounds on patients with severe dry skin are summarized as follows:

5 4+ Effectiveness; glycolic acid, lactic acid, methylactic acid, mandelic acid, tropic acid, atrolactic acid and pyruvic acid.

3+ Effectiveness; benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid, saccharic acid, phenyllactic acid, phenylpyruvic acid, glucuronic acid and 3-hydroxybutanoic acid.

10 2+ Effectiveness; mucic acid, ribonolactone, 2-hydroxydodecanoic acid, guinic acid and benzoylformic acid.

3. Psoriasis.

15 The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. The degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows.

DEGREE OF IMPROVEMENT					
	None (0)	Mild (1 +)	Moderate (2 +)	Substantial (3 +)	Complete (4 +)
25 THICKNESS	Highly elevated	Detectable reduction	Readily apparent reduction	Barely elevated	Normal thickness
TEXTURE	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth
COLOR	Intense Red	Red	Dark Pink	Light Pink	Normal Skin Color

30 By means of such parameters, degree of improvement in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another.

35 Patients having psoriasis participated in this study. Amphoteric and pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and a corticosteroid were prepared according to the Examples. Compositions containing only a corticosteroid were also prepared and included in the comparison test. Test areas were kept to minimal size convenient for topical application, i.e., circles approximately 4 cm in diameter. The medicinal compositions were topically applied by the patient in an amount (usually about 0.1 milliliter) sufficient to cover the test site. Applications were made two to three times daily and without occlusive dressings. Test periods usually lasted for two to four weeks. The test results on patients having psoriasis are summarized on the following table.

Topical Effects on Psoriasis of Antipsoriatic Compositions

45

Compositions*

Therapeutic Effectiveness

50

Hydrocortisone 2.5% alone

1+

With lactic acid

2+

55

With glycolic acid

2+

Compositions*	Therapeutic Effectiveness

5	With benzoic acid 2+
	With pyruvic acid 2+
10	With methylactic acid 2+
	Hydrocortisone 17-valerate 0.2% alone 2+
	With lactic acid 3+
15	With glycolic acid 3+
	With benzoic acid 3+
20	With gluconolactone 3+
	With pyruvic acid 3+
	Betamethasone dipropionate 0.05% alone 3+
25	With lactic acid 4+
	With glycolic acid 4+
30	With mandelic acid 4+
	With benzoic acid 4+
	Clobetasol propionate 0.05% alone 3+
35	With lactic acid 4+
	With glycolic acid 4+

40

45

50

55

	Compositions*	Therapeutic Effectiveness
5	With methylactic acid	4+
	With mandelic acid	4+
10	With tropic acid	4+
	With benzilic acid	4+

15
* Except the "alone" preparations, all others were
amphoteric or pseudoamphoteric compositions containing
20 0.2 to 2M alpha hydroxyacids or related compounds.

We have also found that an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound in combination with an antimetabolite agent such as 5-fluorouracil with
25 or without additional incorporation of a corticosteroid is therapeutically effective for topical treatment of psoriasis.

4. Eczema.

30 In a topical treatment of eczema patients, hydrocortisone alone at 2.5% or hydrocortisone 17-valerate alone at 0.2% would achieve only 2+ improvement, and betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+ improvement on all the eczema patients tested. Test results of amphoteric and pseudoamphoteric compositions containing both a corticosteroid and one of the following alpha hydroxyacids or the related compounds are shown as follows:

35 3+ Effectiveness; hydrocortisone 2.5% or hydrocortisone 17-valerate 0.2% plus lactic acid, glycolic acid, mandelic acid, gluconolactone, benzilic acid or ribonolactone.

4+ Effectiveness; betamethasone dipropionate or clobetasol propionate 0.05% plus lactic acid, glycolic acid, mandelic acid, benzilic acid, gluconolactone, citric acid, tartaric acid or methylactic acid.

40 5. Oily Skin and Skin Cleanse.

Human subjects having oily skin or blemished skin as well as acne patients having extremely oily skin participated in this study. Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds were formulated in solution or gel form.

45 Each participating subject received a solution or a gel preparation containing an alpha hydroxyacid or a related compound in an amphoteric or pseudoamphoteric composition. The participating subjects were instructed to apply topically the solution or gel medication on the affected areas of forehead or other part of the face. Three times daily applications were continued for 2 to 6 weeks.

The degree of improvement of oily skin as well as the rate of improvement of acne lesions were
50 clinically evaluated. Most participants reported that oiliness of skin disappeared within one to two weeks of topical administration, and the skin so treated became smooth and soft. Many participating subjects preferred gel preparations than solution compositions. It was found that all the participants showed substantial improvements on oily skin and acne lesions by six weeks of topical administration of amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant
55 invention.

Those alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for oily skin and as skin cleansers include: benzilic acid, glycolic acid, lactic acid, methylactic acid, mandelic acid, pyruvic acid, tropic acid, malic acid, gluconolactone, 3-hydroxybutanoic acid, glycolide

and polyglycolic acid. As a skin cleanser for oily skin or acne-prone skin, the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may also be incorporated with other dermatologic agents. For example, an amphoteric gel composition may consist of both an alpha hydroxyacid and erythromycin or tetracycline.

5

6. Acne

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention in a solution or gel form were provided to patients having comedogenic and/or papulopustular lesions of acne. Each participating patient was instructed to apply topically the composition on the involved areas of the skin such as forehead, face and chest. Three times daily administration was continued for 6 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated. It was found that acne lesions consisting mainly of comedones improved substantially after 6 to 8 weeks of topical administration with the amphoteric or the pseudoamphoteric composition containing an alpha hydroxyacid or the related compound. The time for complete clearing of comedogenic acne treated with the amphoteric or pseudoamphoteric composition of the instant invention varied from 6 to 12 weeks.

As a topical treatment for papulopustular and/or pustular acne the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may incorporate in addition an antiacne agent. The antiacne agents include antibiotics such as erythromycin, tetracycline, clindamycin, meclocycline and minocycline, and retinoids such as retinoic acid. Such combination compositions have been found to be therapeutically more effective for topical treatment of severe acne.

7. Age Spots

25

Many small and large discolored lesions, commonly called age spots on the face and the back of the hands are benign keratoses, if they are not variants of actinic keratoses. Very few of such age spots are true lentigines, therefore alpha hydroxyacids and the related compounds may be effective in eradicating most age spots without concurrent use of skin bleaching agents such as hydroquinone and monobenzone. However, additional beneficial effects have been found when a skin bleaching agent such as hydroquinone or monobenzone is also incorporated into the compositions of the instant invention for age spots involving pigmented lesions.

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, with or without incorporation of hydroquinone were provided to volunteer subjects and patients having age spot keratoses, melasma, lentigines and/or other pigmented lesions. Each participating subject received two products, i.e., with or without the addition of 2% hydroquinone to the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound.

The volunteer subjects and patients were instructed to apply topically one medication on one side of the body such as left side of the face or on the back of the left hand, and the other medication on the other side of the body such as on right side of the face or on the back of the right hand. Specific instructions were given to the participating subjects that the medications were applied three times daily to the lesions of age spot keratoses, melasmas, lentigines and/or other pigmented lesions. Clinical photos were taken of participating subjects before the initiation of the topical treatment and every 4 weeks during the course of treatment.

At the end of 4 to 8 weeks, improvement of age spot keratoses was clinically discernible. After 4 to 6 months of topical treatment, substantial improvement of age spot keratoses occurred in the majority of subjects tested. Complete eradication of age spot keratoses occurred after 6 to 9 months of topical administration with the amphoteric or pseudoamphoteric compositions of the instant inventions.

Amphoteric or pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and hydroquinone were judged to be more effective in eradicating pigmented age spots, melasma, lentigines and other pigmented lesions.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for age spots with or without combination with hydroquinone include glycolic acid, lactic acid, methylactic acid, mandelic acid, pyruvic acid, benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid and tropic acid. For flat or slightly elevated seborrheic keratoses on the face and/or the back of the body, amphoteric or pseudoamphoteric compositions containing higher concentrations of alpha hydroxyacids or the related compounds have been found to be effective in eradicating such lesions.

Actinic keratoses may be successfully treated with amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds in combination with an antimetabolite agent such as 5-fluorouracil.

5 8. Warts.

Eradications of common warts by topical application of amphoteric or pseudoamphoteric compositions require higher than usual concentrations of alpha hydroxyacids or the related compounds in the formulations. The amphoteric or pseudoamphoteric compositions were formulated as a liquid or light gel form, and
10 dispensed usually as 0.5-1 ml aliquots in small vials.

Topical applications were made discreetly to wart lesions by adult patients or by responsible adult family members. For ordinary usual warts of hands, fingers, palms and soles topical applications were made 2 to 4 times daily, and were continued for 2 to 6 weeks. Generally, the overlying stratum corneum of the wart lesion change in appearance after several weeks topical application of the composition. In most cases,
15 the wart lesion simply fell off. The skin then healed normally without forming any scars.

We have also found that when a dermatologic agent such as 5-fluorouracil is incorporated into the amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, the medications have been very effective for topical treatment of warts without using higher concentrations of alpha hydroxyacids or the related compounds.

20 The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for topical treatment of warts with or without incorporation of 5-fluorouracil include glycolic acid, lactic acid, pyruvic acid, and mandelic acid.

Topical formulations and compositions containing specific alpha hydroxyacids, alpha ketoacids or the related compounds at full strengths or high to intermediate concentrations prepared according to Examples
25 54 and 55, without utilizing amphoteric or pseudoamphoteric systems, have also been tested for ordinary warts of the hands, fingers, palms and soles. Participating patients have been advised to apply a small drop of the medication with a toothpick or a fine caliber brush to the center of a wart lesion only. Prescribed applications have been 3 to 6 times daily, and are continued until the patient feels pain.

For the more rough-surfaced wart, the duration of application has been as short as one or a few days.
30 For lesions with more compact, less permeable stratum corneum, the time to experience pain has been longer. Frequency and duration of applications have been modified according to other clinical responses and reactions of lesions, and the patient or responsible family member is instructed accordingly.

For example, some clinical manifestations other than pain have also been used as a signal to interrupt application. These manifestations have included distinct blanching of the lesions or distinct peripheral
35 erythema. Very often, discomfort is the usual signal of clinical reactions.

Generally, the overlying stratum corneum of the wart lesions became loose, and the whole wart lesion simply fell off. The skin then healed normally without forming any scars.

9. Athlete's Foot and Nail Infections

40 Amphoteric and pseudoamphoteric compositions containing both an antifungal agent and one of the alpha hydroxyacids or the related compounds were provided to patients having frequent recurrence of fungal infections involving the foot. The antifungal agents include clotrimazole, miconazole, ketoconazole and griseofulvin. When both feet but not toe nails were involved in the infection, the patients were instructed
45 to apply topically the compositions of the instant invention on the left foot, and a brand-name antifungal product on the right foot. Three times daily applications were continued for one to four weeks. The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the amphoteric or pseudoamphoteric compositions containing both the antifungal agent and the alpha hydroxyacid or the
50 related compound. The alpha hydroxyacids or the related compounds seemed to enhance the efficacies of the antifungal agents, and also to eliminate the discomforts such as itching, tingling, burning and irritation due to fungal infections. When toe nails were not involved the infected skin generally healed within one to two weeks from topical application of the amphoteric or pseudoamphoteric composition containing both an antifungal agent and an alpha hydroxyacid or the related compound.

55 Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When toe nails were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in com-

bination an antifungal agent and an alpha hydroxyacid or an alpha ketoacid at higher concentrations ranging from 20 to 99%, dispensed as 1-2 ml aliquots in small vials. The patients were instructed to apply topically the compositions discreetly to the infected nail surface by means of a fine calibre paint brush. the technique was the same as for application of nail polish, that is careful avoidance of contact with lateral nail folds or any peri-ungual skin. Once or twice daily applications were continued for 2 to 8 weeks.

As mentioned above, while brand-name antifungal products are usually not effective against fungus infections within or underneath the nail, it was found that the amphoteric or pseudoamphoteric compositions containing an antifungal agent and an alpha hydroxyacid or alpha ketoacid were therapeutically effective in eradicating fungal infections of the nails. Such treatment may cause in some instances the treated nail plate to become loose and eventually fell off from the nail bed. This happened quite naturally without any feeling of pain nor bleeding, and the skin lesion healed quickly with normal growth of a new nail.

10. Wrinkles

Wrinkles of skin may be due to natural aging and/or sun damage. Most fine wrinkles on the face are due to natural or innate aging, while coarse wrinkles on the face are the consequence of actinic or sun damage. Although the real mechanism of wrinkles formation in the skin is still unknown, it has been shown that visible fine wrinkles are due to diminution in the number and diameter of elastic fibers in the papillary dermis, and also due to atrophy of dermis as well as reduction in subcutaneous adipose tissue. Histopathology and electron microscopy studies indicate that coarse wrinkles are due to excessive deposition of abnormal elastic materials in the upper dermis and thickening of the skin. At present there are no commercial products which have been found to be therapeutically effective for topical eradication of wrinkles, although retinoic acid (tretinoin) has been shown to be beneficial for sun damaged skin.

In order to determine whether the amphoteric or pseudoamphoteric composition containing the alpha hydroxyacids, alpha ketoacids or the related compounds are therapeutically effective for wrinkles, patients and volunteer subjects participated in this study. The participants were instructed to apply the formulations of the instant invention twice daily on areas of facial wrinkles for 4 to 12 months. All participants were told to avoid sun exposure, and to use sunscreen products if exposure to sunlight was unavoidable. Photographs of each side of the face for each participant were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear any facial make-up at the time of each office visit. Standardized photographic conditions were used including the use of same lot of photographic film, the same light source at two feet from the face, aimed at a locus on the frontal aspect of each cheek. Each time photographs were taken with camera aimed perpendicular to the cheek. At the end of study twenty two participants had been entered into the study for at least four months. Clinical evaluations and review of photographs have revealed substantial reductions in facial wrinkles of the temporal region and cheek area on at least one side of the face in eighteen cases. Degree of improvement and reduction in wrinkles has been evaluated and determined to be mild to moderate in six participants but very substantial in twelve participants.

The alpha hydroxyacids, alpha ketoacids and other related compounds including their lactone forms which may be incorporated into the amphoteric and pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders such as dry skin, acne, age spots, keratoses, warts and skin wrinkles or in combination with other dermatologic agents to enhance therapeutic effects include the following:

(1) Alkyl Alpha Hydroxyacids

2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methylactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid) , 2 - Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid).

(2) Aalkyl And Aryl Alpha Hydroxyacids

2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic

acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid, 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

(3) Polyhydroxy Alpha Hydroxyacids

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2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; aldonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid), 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid, etc.)

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(4) Polycarboxylic Alpha Hydroxyacids

2-Hydroxypropane 1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid, etc.)

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(5) Alpha Hydroxyacid Related Compounds

Ascorbic acid, quinic acid, isocitric acid, tropic acid, 3-chlorolactic acid, trethocanic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid and aleuritic acid.

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(6) Alpha Ketoacids And Related Compounds

2-Ketoethanoic acid (Glyoxylic acid), 2-Ketopropanoic acid (Pyruvic acid), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid and 2-Ketododecanoic acid.

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The amphoteric and pseudoamphoteric compounds which may be incorporated into the compositions of the instant invention for cosmetic and dermatologic conditions include amino acids, peptides, polypeptides, proteins and the like compounds such as creatinine and creatine.

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The dimeric and polymeric forms of alpha hydroxyacids and the related compounds which may be incorporated into the compositions of the instant invention include acyclic esters and cyclic ester; for example, glycolyl glycolate, lactyl lactate, glycolide, lactide, polyglycolic acid and polylactic acid.

35 Claims

Claims for the following Contracting States : AT, BE, CH, DE DK, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical or cosmetic composition for topical application, said composition comprising an active ingredient selected from alpha hydroxyacids, alpha ketoacids, dimeric and polymeric forms of hydroxyacids, ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid, pantoic acid, lactones derived from said acids and salts of said acids with organic bases or inorganic alkalis, in a pharmaceutically acceptable vehicle for topical application, characterized in that the composition comprises an amphoteric system consisting essentially of said active ingredient in combination with an amphoteric or pseudoamphoteric organic compound, which acts to raise the overall pH of the composition.
2. A composition according to claim 1 further comprising an additional cosmetic or pharmaceutical agent in said composition.
3. A composition according to claim 2 wherein said additional cosmetic or pharmaceutical agent is selected from agents that improve or eradicate age spots; keratoses and wrinkles; analgesics; anaesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; anti-motion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditions and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids;

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topical cardiovascular agents or dermatologicals.

4. A composition according to claim 3 wherein said additional cosmetic or pharmaceutical agent is selected from clotrimazole, ketoconazole, minconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone, monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retionic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotonamiton, propranolol, promethazine, vitamin A palmitate or vitamin E acetate.
5. A composition according to any preceding claim wherein the amphoteric or pseudoamphoteric substance is selected from amino acids, peptides, polypeptides, proteins, imidazoline derivatives and lecithin derivatives.
6. A composition according to any preceding claim wherein the amphoteric or pseudoamphoteric substance is selected from glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, creatinine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, theanine, phenylglycine, canavanine, cananine, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β -lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, 2-methylserine, 3-phenylserine, taurine, cysteinesulfonic acid, methionine sulfoxide, methionine sulfone, 3,5-diiodotyrosine, thyroxine, moniodotyrosine, pipecolic acid, 4-aminopipecolic acid, 4-methylproline, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β -alanyllysine, β -alanylarginine, glutathione, ophthalmic acid, norophthalmic acid, bradykinin, glucagon, protamines, histones, cocoamphoglycine, cocoamphopropionate, cocoamphopropysulfonate, phosphatidyl ethanolamine, phosphatidyl serine, sphingomyelin, aminoaldonic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.
7. A composition according to any one of claims 1 to 6 wherein the amphoteric compound has at least one acidic and one basic group in the molecule.
8. A composition according to claim 7 wherein the amphoteric compound is arginine.
9. A composition according to claim 7 wherein the amphoteric compound is lysine.
10. A composition according to claim 7 wherein the amphoteric compound is glycine.
11. A composition according to claim 7 wherein the pseudoamphoteric compound is creatinine.
12. A composition according to any preceding claim wherein said α -hydroxyacid is selected from alkyl α -hydroxyacids, aralkyl and aryl α -hydroxyacids, polyhydroxy α -hydroxyacids and polycarboxylic α -hydroxyacids having the following chemical formula:

$$(Ra) (Rb) C (OH) COOH$$

wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said α -hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.
13. A composition according to claim 12 wherein said alkyl α -hydroxyacid is selected from 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), methyl 2-hydroxypropanoic acid (methyl lactic acid), 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-

hydroxyheptanoic acid, 2-hydroxyoctanoic acid, 2-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxyundecanoic acid, 2-hydroxydodecanoic acid (α -hydroxylauric acid), 2-hydroxytetradecanoic acid (α -hydroxymyristic acid), 2-hydroxyhexadecanoic acid (α -hydroxypalmitic acid), 2-hydroxyoctadecanoic acid (α -hydroxystearic acid), 2-hydroxyeicosanoic acid (α -hydroxyarachidonic acid).

- 5 14. A composition according to claim 13 wherein the α -hydroxy acid is glycolic acid.
- 15 15. A composition according to claim 13 wherein the α -hydroxy acid is lactic acid.
- 10 16. A composition according to claim 13 wherein the α -hydroxy acid is methylactic acid.
- 15 17. A composition according to claim 12 wherein said aralkyl or aryl α -hydroxy acid is selected from 2-phenyl 2-hydroxyethanoic acid (mandelic acid), 2,2-diphenyl 2-hydroxyethanoic acid (benzilic acid), 3-phenyl 2-hydroxypropanoic acid (phenyllactic acid), 2-phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid), 2-(4'-hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-hydroxyphenyl) 2-hydroxypropanoic acid 3-(4'-hydroxyphenyl) 2-hydroxypropanoic acid, or 2-(3',4'-dihydroxyphenyl) 2-hydroxyethanoic acid.
- 20 18. A composition according to claim 12 wherein said polyhydroxy α -hydroxyacid or polycarboxylic α -hydroxyacid is selected from 2, 3-dihydroxypropanoic acid (glyceric acid), 2,3,4-trihydroxybutanoic acid (isomers: erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (isomers: ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-pentahydroxyhexanoic acid (isomers: allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid), 25 2,3,4,5,6,7-hexahydroxyheptanoic acid (isomers: glucoheptonic acid, galactoheptonic acid), 2-hydroxypropane -1,3-dioic acid (tartronic acid), 2-hydroxybutane-1,4-dioic acid (malic acid), 2,3-dihydroxybutane-1,4-dioic acid (tartaric acid), 2-hydroxy-2-carboxypentane-1,5-dioic acid (citric acid), 2,3,4,5-tetrahydroxyhexane-1,6-dioic acid (isomers: saccharic acid, mucic acid), or lactone forms (gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, galactoheptonolactone)
- 30 19. A composition according to claim 18 wherein said α -hydroxyacid is citric acid.
20. A composition according to claim 18 wherein said α -hydroxyacid is tartaric acid.
- 35 21. A composition according to claim 18 wherein said α -hydroxyacid is malic acid.
22. A composition according to claim 18 wherein said active ingredient is gluconolactone.
- 40 23. A composition according to any preceding claim wherein said alpha ketoacid has the following chemical formula:

R-CO-COOH

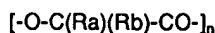
45 wherein R represents H or an alkyl, aralkyl or aryl group of saturated or unsaturated isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition R may carry F, Cl, Br, I, OH, CHO, COOH or an alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali.
- 50 24. A composition according to claim 23 wherein said α -ketoacid is selected from 2-ketoethanoic acid (glyoxylic acid), 2-ketopropanoic acid (pyruvic acid), 2-phenyl-2-ketoethanoic acid (benzoylformic acid), 3-Phenyl-2-ketopropanoic acid (phenylpyruvic acid), 2-ketobutanoic acid, 2-ketopentanoic acid, 2-ketohexanoic acid, 2-ketoheptanoic acid, 2-ketooctanoic acid or, 2-ketododecanoic acid.
- 55 25. A composition according to any preceding claim wherein said active ingredient is selected from dimeric or polymeric forms of hydroxyacids having the following chemical formula:



wherein Ra,Rb = H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n = 2 or any numerical number up to 200; Ra and Rb in monomer unit 2, 3, 4 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms, and the dimeric and polymeric forms of hydroxyacids may be present as a free acid, or in a salt form with an organic base or inorganic alkali.

26. A composition according to claim 25 wherein said dimeric or polymeric forms of hydroxyacids are selected from glycolyl glycollate, lactyl lactate, mandelyl mandellate, atrolactyl atrolactate, phenyllactyl phenyllactate, benzilyl benzillate, glycolyl lactate, lactyl glycollate, triglycolic acid, trilactic acid, polyglycolic acid or polylactic acid.

27. A composition according to any one of claims 1 to 24 wherein said active ingredient is selected from dimeric or polymeric forms of hydroxyacids, having the following chemical formula:



wherein Ra, Rb = H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n = 2 or any numerical number, and Ra or Rb may be identical or not identical in the monomer units.

28. A composition according to claim 27 wherein said dimeric or polymeric forms of hydroxyacids are selected from glycolide, lactide, mandelide, atrolactide phenyllactide, benzilide, methylactide, lactoglycolide or glycolactide.

29. A composition according to any preceding claim for use in the treatment of dry skin, zerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne, warts, eczema, puritic skin, psoriasis, inflammatory dermatoses, disturbed keratinization, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair or scalp requiring shampooing or conditioning.

30. A cosmetic skin treatment which comprises the topical application to the skin of a composition according to any preceding claim.

31. The use in the preparation of a pharmaceutical or cosmetic composition for the topical treatment of skin conditions, of an amphoteric system as defined in claim 1.

32. A method for controlling the acidity of a pharmaceutical or cosmetic composition for topical application of the type wherein an active ingredient selected from alpha hydroxyacids, alpha ketoacids, dimeric and polymeric forms of hydroxyacids, ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid, pantoic acid, lactones derived from said acids and salts of said acids with organic bases or inorganic alkalis is mixed with a pharmaceutically acceptable vehicle for topical application, characterised in that an amphoteric or pseudoamphoteric organic compound is added to the mixture to raise the overall pH of the composition and form an amphoteric system by combining with said active ingredient.

33. A method according to claim 32 wherein said amphoteric compound has at least one basic and one acidic group in the molecule.

34. A method according to claim 33 wherein said amphoteric compound is selected from arginine, glycine and lysine.

35. A method according to claim 32 wherein said pseudoamphoteric compound is creatinine.

36. A method according to any one of claims 32 to 35, wherein the α -hydroxyacid is lactic acid.

Claims for the following Contracting States : ES, GR

1. A method of making a pharmaceutical or cosmetic composition for topical application, wherein an active ingredient selected from alpha hydroxyacids, alpha ketoacids, dimeric and polymeric forms of hydroxyacids, ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid, pantoic acid, lactones derived from said acids and salts of said acids with organic bases or inorganic alkalis is mixed with a pharmaceutically acceptable vehicle for topical application, characterized in that an amphoteric or pseudoamphoteric organic compound is added to the mixture to raise the overall pH of the composition and form an amphoteric system by combining with said active ingredient.
2. A method according to claim 1 wherein said amphoteric compound has at least one basic and one acidic group in the molecule.
3. A method according to claim 1 or claim 2 further comprising an additional cosmetic or pharmaceutical agent in said composition.
4. A method according to claim 3 wherein said additional cosmetic or pharmaceutical agent is selected from agents that improve or eradicate age spots; keratoses and wrinkles; analgesics; anaesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; anti-motion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidry skin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditions and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents or dermatologicals.
5. A method according to claim 3 wherein said additional cosmetic or pharmaceutical agent is selected from clotrimazole, ketoconazole, minconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, hydroquinone, monobenzene, erythromycin, tetracycline, clindamycin, meclocycline, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retionic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate or vitamin E acetate.
6. A method according to any preceding claim wherein the amphoteric or pseudoamphotoeric substance is selected from amino acids, peptides, polypeptides, proteins, imidazoline derivatives, lecithin derivatives, zinc oxide and aluminium oxide.
7. A method according to any preceding claim wherein the amphoteric or pseudoamphoteric substance is selected from glycine, alanine, valine leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine ornithine, citrulline, creatine, creatinine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, theanine, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β -lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, 2-methylserine, 3-phenylserine, taurine, cysteinesulfinic acid, methionine sulfoxide, methionine sulfone, 3,5-diiodotyrosine, thyroxine, monoiodotyrosine, pipelicolic acid, 4-aminopipelicolic acid, 4-methylproline, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β -alanyllysine, β -alanylarginine, glutathione, ophthalmic acid, norophthalmic acid, bradykinin, glucagon, protamines, histones, cocoamphoglycine, cocoamphopropionate, cocoamphopropysulfonate, phosphatidyl ethanolamine, phosphatidyl serine sphingomyelin, aminoaldonic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated heparin deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.
8. A method according to claim 7 wherein the amphoteric compound is arginine.

9. A method according to claim 7 wherein the amphoteric compound is lysine.
10. A method according to claim 7 wherein the amphoteric substance is glycine.
11. A method according to claim 7 wherein the pseudoamphoteric compound is creatinine.
12. A method according to any preceding claim wherein said α -hydroxyacid is selected from alkyl α -hydroxyacids, aralkyl and aryl α -hydroxyacids, polyhydroxy α -hydroxyacids and polycarboxylic α -hydroxyacids having the following chemical formula:

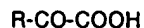
(Ra) (Rb) C (OH) COOH

wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.
13. A method according to claim 12 wherein said alkyl α -hydroxyacid is selected from 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), methyl 2-hydroxypropanoic acid (methyl lactic acid), 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxyoctanoic acid, 2-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxyundecanoic acid, 2-hydroxydodecanoic acid (α -hydroxylauric acid), 2-hydroxytetradecanoic acid (α -hydroxymyristic acid), 2-hydroxyhexadecanoic acid (α -hydroxypalmitic acid), 2-hydroxyoctadecanoic acid (α -hydroxystearic acid), 2-hydroxyeicosanoic acid (α -hydroxyarachidonic acid).
14. A method according to claim 13 wherein the α -hydroxy acid is glycolic acid.
15. A method according to claim 14 wherein the α -hydroxy acid is lactic acid.
16. A method according to claim 13 wherein the α -hydroxy acid is methyl lactic acid.
17. A method according to claim 12 wherein said aralkyl or aryl α -hydroxy acid is selected from 2-phenyl 2-hydroxyethanoic acid (mandelic acid), 2,2-diphenyl 2-hydroxyethanoic acid (benzilic acid), 3-phenyl 2-hydroxypropanoic acid (phenyllactic acid), 2-phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid), 2-(4'-hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-hydroxyphenyl) 2-hydroxypropanoic acid 3-(4'-hydroxyphenyl) 2-hydroxypropanoic acid, or 2-(3',4'-dihydroxyphenyl) 2-hydroxyethanoic acid.
18. A method according to claim 12 wherein said polyhydroxy α -hydroxyacid or polycarboxylic α -hydroxyacid is selected from 2, 3-dihydroxypropanoic acid (glyceric acid), 2,3,4-trihydroxybutanoic acid (isomers: erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (isomers: ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-pentahydroxyhexanoic acid (isomers: allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid), 2,3,4,5,6,7-hexahydroxyheptanoic acid (isomers: glucoheptonic acid, galactoheptonic acid), 2-hydroxypropane-1,3-dioic acid (tartronic acid), 2-hydroxybutane-1,4-dioic acid (malic acid), 2,3-dihydroxybutane-1,4-dioic acid (tartaric acid), 2-hydroxy-2-carboxypentane-1,5-dioic acid (citric acid), 2,3,4,5-tetrahydroxyhexane-1,6-dioic acid (isomers: saccharic acid, mucic acid), or lactone forms (gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, galactoheptonolactone).
19. A method according to claim 18 wherein said α -hydroxyacid is citric acid.
20. A method according to claim 18 wherein said α -hydroxyacid is tartaric acid.
21. A method according to claim 18 wherein said α -hydroxyacid is malic acid.

22. A method according to claim 18 wherein said active ingredient is gluconolactone.

23. A method according to any preceding claim wherein said alpha ketoacid has the following chemical formula:

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wherein R represents H or an alkyl, aralkyl or aryl group of saturated or unsaturated isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition R may carry F, Cl, Br, I, OH, CHO, COOH or an alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or in a salt form with an organic base or an inorganic alkali.

24. A method according to claim 23 wherein said α -ketoacid is selected from 2-ketoethanoic acid (glyoxylic acid), 2-ketopropanoic acid (pyruvic acid), 2-phenyl-2-ketoethanoic acid (benzoylformic acid), 3-Phenyl-2-ketopropanoic acid (phenylpyruvic acid), 2-ketobutanoic acid, 2-ketopentanoic acid, 2-ketohexanoic acid, 2-ketoheptanoic acid, 2-ketooctanoic acid or, 2-ketododecanoic acid.

25. A method according to any preceding claim wherein said active ingredient is selected from dimeric or polymeric forms of hydroxyacids having the following chemical formula:

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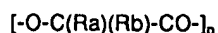


wherein Ra,Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=2 or any numerical number up to 200; Ra and Rb in monomer unit 2, 3, 4 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms, and the dimeric and polymeric forms of hydroxyacids may be present as a free acid, or in a salt form with an organic base or inorganic alkali.

26. A method according to claim 25 wherein said dimeric or polymeric forms of hydroxyacids are selected from glycolyl glycollate, lactyl lactate, mandelyl mandellate, atrolactyl atrolactate, phenyllactyl phenyllactate, benzilyl benzillate, glycolyl lactate, lactyl glycollate, triglycolic acid, trilactic acid, polyglycolic acid or polylactic acid.

27. A method according to any one of claims 1 to 24 wherein said active ingredient is selected from dimeric or polymeric forms of hydroxyacids, having the following chemical formula:

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wherein Ra, Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=2 or any numerical number, and Ra or Rb may be identical or not identical in the monomer units.

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28. A method according to claim 27 wherein said dimeric or polymeric forms of hydroxyacids are selected from glycolide, lactide, mandelide, atrolactide phenyllactide, benzilide, methyllactide, lactoglycolide or glycolactide.

29. A cosmetic skin treatment which comprises the topical application to the skin of a composition made by a method according to any preceding claim.

30. The use in the preparation of a pharmaceutical or cosmetic composition for the topical treatment of skin conditions, of an amphoteric system as defined in claim 1.

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Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische oder kosmetische Zusammensetzung zur lokalen Anwendung, wobei diese Zusammensetzung umfaßt einen aktiven Bestandteil, ausgewählt aus alpha-Hydroxy-Säuren, alpha-Keto-Säuren, dimerischen und polymeren Hydroxy-Säuren, Ascorbin-Säure, Quinic-Säure, Isocitric-Säure, Tropic-Säure, Trethocanic-Säure, 3-Chlorolactic-Säure, Cerebronic-Säure, Citramalic-Säure, Agaricic-Säure, 2-Hydroxy-Nervonic-Säure, Aleuretic-Säure, Pantoic-Säure, von diesen Säuren abgeleiteten Lactonen und Salzen dieser Säuren mit organischen Basen oder anorganischen Alkaliden, in einem pharmazeutisch akzeptierbaren Träger zur lokalen Anwendung, dadurch gekennzeichnet, daß die Zusammensetzung ein amphoterer System enthält, das im wesentlichen aus diesem aktiven Bestandteil in Kombination mit einer amphoteren oder pseudo-amphoteren organischen Komponente besteht, die wirkt, um den Gesamt-pH-Wert der Zusammensetzung zu heben.
2. Zusammensetzung nach Anspruch 1, die weiter einen zusätzlichen kosmetischen oder pharmazeutischen Wirkstoff in dieser Zusammensetzung umfaßt.
3. Zusammensetzung nach Anspruch 2, wobei dieser zusätzliche kosmetische oder pharmazeutische Wirkstoff ausgewählt ist aus Wirkstoffen, die Alterflecken, Keratosen und Falten ganz oder teilweise beseitigen; aus Analgestika; Anaesthetiven; Anti-Akne-Wirkstoffen; antibakterielle Wirkstoffen; Anti-Hefe-Wirkstoffen; Anti-Pilz-Wirkstoffen; Anti-Virus-Wirkstoffen; Antischuppen-Wirkstoffen; Antidermatitis-Wirkstoffen; Antipuritis-Wirkstoffen; Antiemetiziden; Anti-Motion-Übelkeit-Wirkstoffen; entzündungshemmenden Wirkstoffen; Anti-Hyperkeratologischen Wirkstoffen; Wirkstoffen gegen trockene Haut; Anti-Schwitzmittel; Anti-Psoriasis-Wirkstoffen; Anti-seborrheischen Wirkstoffen; Wirkstoffen zur Haarbehandlung und Haarbeeinflussung; Anti-Asthma-Wirkstoffen und Bronchialerweiterern; Sonnenschutz-Wirkstoffen; Anti-Histamin-Wirkstoffen; hautaufhellenden Wirkstoffen; Wirkstoffen zur Depigmentierung; Vitaminen; Corticosteroiden; Bräunungs-Wirkstoffen; Hormonen; Retinoiden; lokalen kardiovaskulären Wirkstoffen oder dermatologischen Wirkstoffen.
4. Zusammensetzung nach Anspruch 3, wobei dieser zusätzliche kosmetische oder pharmazeutische Wirkstoff ausgewählt ist aus Clotrimazol, Ketoconazol, Minconazol, Griseofulvin, Procain, Di-Phenhydramin, Parxomin, Lidocain, Mepivacain, Hydroquinon, Mono-Bezon, Erythromycin, Tetracyclin, Clindamycin, Meclocyclin, Minocyclin, Naproxen, Ibuprofen, Theophyllin, Cromolyn, Albuterol, Retin-Säure, 13-cis-Retin-Säure, Hydro-Cortison, Hydro-Cortison 21-Acetat, Hydro-Cortison 17-Valerat, Hydro-Cortison 17-Butyrat, Betamethason-Valerat, Betamethason-Di-Propionat, Triamcinolon-Acetonid, Fluocinonid, Clobetasol-Propionat, Benzyol-Peroxid, Crotamiton, Propranolol, Promethazin, Vitamin A-Palmitat oder Vitamin E-Acetat.
5. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei die amphoterische oder pseudo-amphoterische Substanz ausgewählt ist aus Aminosäuren, Peptide, Polypeptiden, Proteinen, Imidiazolin-Derivaten und Lecithin-Derivaten.
6. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei die amphoterische oder pseudo-amphoterische Substanz ausgewählt ist aus Glycin, Alanin, Valin-Leucin, Iso-Leucin, Serin, Threonin, Cystein, Cystin, Methionin, Aspartic-Säure, Asparagin, Glutamic-Säure, Glutamin, Arginin, Lysin, 5-Hydroxy-Lysin, Histidin, Phenylalanin, Tyrosin, Tryptophan, 3-Hydroxy-Prolin, 4-Hydroxy-Prolin, Prolin, Homocystein, Homocystin, Homoserin-Ornithin, Citrullin, Creatin, Creatinin, 2-Amino-Butonic-Säure, 4-Amino-Butonic-Säure, 2-Amino-2-Methyl-Propanic-Säure, 2-Amino-3-Methyl-Propanic-Säure, Theanin, Phenylglycin, Canavanin, Canalin, 4-Hydroxy-Arginin, 4-Hydroxy-Ornithin, Homoarginin, 4-Hydroxy-Homoarginin, β -Lysin, 2,4-Diamino-Butanoic-Säure, 2,3-Diamino-Propanoic-Säure, 2,6-Diamino-Pimelic-Säure, 2-Amino-3-Phenyl-Butanoic-Säure, 2-Methylserin, 3-Phenylserin, Taurin, Cystein-Sulfinic-Säure, Methioninsulfoxid, Methioninsulfon, 3,5-Diiodo-Tyrosin, Thyroxin, Monoiodo-Tyrosin, Pipecolic-Säure, 4-Amino-Pipecolic-Säure, 4-Methyl-Proline, Glycylglycin, Carnosin, Anserin, Ophidin, Homocarnosin, β -Alanyl-Lysin, β -Alanyl-Arginin, Glutathion, Ophthalmic-Säure, Norophthalmic-Säure, Bradykinin, Glucagon, Protamine, Histone, Co-Co-Ampho-Glycin, Co-Co-Ampho-Propionat, Co-Co-Ampho-Propylsulfonat, Phosphatidyl-Ethanol-Amin, Phosphatidyl-Serin-Sphingomyelin, Aminoaldonic-Säuren, Aminoaldartic-Säuren, Lauryl-Amino-Propyl-Glycin, Meuramic-Säure, entschwefeltes Heparin, deacetylierte Hyaluronic-Säure, Hyalo-Bi-Uronic-Säure, Condrosine und deacetyliertes Chondroitin.

7. Zusammensetzung nach einem der Ansprüche 1 - 6, wobei der amphoterische Bestandteil wenigstens eine Säuregruppe und eine Basengruppe in dem Molekül aufweist.
8. Zusammensetzung nach Anspruch 7, wobei der amphoterische Bestandteil Arginin ist.
9. Zusammensetzung nach Anspruch 7, wobei der amphoterische Bestandteil Lysin ist.
10. Zusammensetzung nach Anspruch 7, wobei der amphoterische Bestandteil Glycin ist.
11. Zusammensetzung nach Anspruch 7, wobei der amphoterische Bestandteil Creatinin ist.
12. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei diese α -Hydroxy-Säure ausgewählt ist aus Alkyl- α -Hydroxy-Säuren, Arakyl- und Aryl- α -Hydroxy-Säuren, Poly-Hydroxy- α -Hydroxy-Säuren und Poly-Carboxylic- α -Hydroxy-Säuren mit der folgenden chemischen Formel:
- $$(Ra) (Rb) C (OH) COOH$$
- wobei Ra und RB H, F, Cl, Br, Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form sind, die 1 bis 25 C-Atome aufweisen, und zusätzlich können Ra und Rb OH, CHO, COOH und eine Alkoxy-Gruppe mit 1 bis 9 C-Atomen tragen, wobei diese α -Hydroxy-Säure als freie Säure oder in Lactonform vorliegt, oder in Form eines Salzes mit organischer Base oder als anorganisches Alkali, und als Stereoisomere als D-, L- und DL-Formen, wenn Ra und Rb nicht identisch sind.
13. Zusammensetzung nach Anspruch 12, wobei diese Alkyl- α -Hydroxy-Säure ausgewählt ist aus 2-Hydroxy-Ethanoic-Säure Glycol-Säure), 2-Hydroxy-Propanic-Säure (Milchsäure), Methyl-2-Hydroxy-Propanoic-Säure (Methylmilchsäure), 2-Hydroxy-Butanoic-Säure, 2-Hydroxy-Pentanoic-Säure, 2-Hydroxy-Hexanoic-Säure, 2-Hydroxy-Heptanoic-Säure, 2-Hydroxy-Octanoic-Säure, 2-Hydroxy-Nonanoic-Säure, 2-Hydroxy-Decanoic-Säure, 2-Hydroxy-Undecanoic-Säure, 2-Hydroxy-Dodecanoic-Säure, (α -Hydroxy-Lauric-Säure), 2-Hydroxy-Tetradecanoic-Säure (α -Hydroxy-Myristic-Säure), 2-Hydroxy-Hexadecanoic-Säure(α -Hydroxy-Palmitic-Säure), 2-Hydroxy-Octadecanoic-Säure(α -Hydroxy-Stearic-Säure), 2-Hydroxy-Eicosanoic-Säure(α -Hydroxy-Arachidonic-Säure).
14. Zusammensetzung nach Anspruch 13, wobei die α -Hydroxy-Säure Glycol-Säure ist.
15. Zusammensetzung nach Anspruch 13, wobei die α -Hydroxy-Säure Milchsäure ist.
16. Zusammensetzung nach Anspruch 13, wobei die α -Hydroxy-Säure Methylmilchsäure ist.
17. Zusammensetzung nach Anspruch 12, wobei diese Arakyl- oder Aryl- α -Hydroxy-Säure ausgewählt ist von 2-Phenyl 2-Hydroxy-Ethanoic-Säure (Mandelsäure), 2,2-Diphenyl-2-Phenyl-2-Hydroxy-Ethanoic-Säure (Benzilic-Säure), 3-Phenyl 2-Hydroxy-Propanoic-Säure (Phenylmilchsäure), 2-Phenyl 2-methyl 2-Hydroxy-Ethanoic-Säure (Atromilchsäure), 2-(4'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-(4'-Chloro-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-(3'-Hydroxy-4'-Methoxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-Hydroxy-Ethanoic-Säure, 2-(4'-Hydroxy-3'-Methoxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 3-(2'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 3-(4'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure oder 2-(3',4'-Dihydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure.
18. Zusammensetzung nach Anspruch 12, wobei diese Polyhydroxy α -Hydroxy-Säure oder die Polycarboxyl α -Hydroxy-Säure ausgewählt ist aus 2, 3-Dihydroxy-Propanoic-Säure (Glycerinsäure), 2,3,4-Trihydroxy-Butanoic-Säure (Isomere: Erythron-Säure, Threon-Säure), 2,3,4,5-Tetrahydroxy-Pentanoic-Säure (Isomere: Ribonic-Säure, Arabionic-Säure, Xylonic-Säure, Lysonic-Säure), 2,3,4,5,6-Pentahydroxy-Hexanoic-Säure (Isomere: Allonic-Säure, Altronic-Säure, Gluconic-Säure, Mannonic-Säure, Gulonic-Säure, Idonic-Säure, Galactonic-Säure, Talonic-Säure), 2,3,4,5,6,7-Hexahydroxy-Heptanoic-Säure (Isomere: Glucoheptonic-Säure, Galactoheptonic-Säure), 2-Hydroxy-Propan - 1,3-Dioic-Säure (Tartronic-Säure), 2-Hydroxy-Butan-1,4-Dioic-Säure (Malic-Säure), 2,3-Dihydroxy-Butan-1,4-Dioic-Säure (Tartaric-Säure), 2-Hydroxy-2-Carboxy-Pentan-1,5-Dioic-Säure (Zitronensäure), 2,3,4,5-Tetrahydroxy-Hexan-1,6-Dioic-Säure (Isomere: Saccharic-Säure, Mucic-Säure) oder Lactonformen (Glucono-Lacton, Galactono-Lacton,

Glucurono-Lacton, Galacturono-Lacton, Gulono-Lacton, Ribono-Lacton, Saccharic-Säure-Lacton, Pantoyl-Lacton, Glucoheptono-Lacton, Mannono-Lacton, Galactoheptono-Lacton).

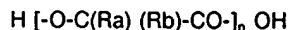
19. Zusammensetzung nach Anspruch 18, wobei diese α -Hydroxy-Säure Zitronensäure ist.
20. Zusammensetzung nach Anspruch 18, wobei diese α -Hydroxy-Säure Tartaric-Säure ist.
21. Zusammensetzung nach Anspruch 18, wobei diese α -Hydroxy-Säure Malic-Säure ist.
22. Zusammensetzung nach Anspruch 18, wobei diese α -Hydroxy-Säure Glucono-Lacton ist.
23. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei diese alpha Keto-Säure die folgende chemische Formel aufweist:



wobei R H oder Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellt, die 1 bis 25 C-Atome aufweisen, und zusätzlich kann R F, Cl, Br, I, OH, CHO, COOH oder eine Alkoxy-Gruppe mit 1 bis 9 C-Atomen tragen, wobei diese alpha-Heto-Säure als freie Säure oder in Form eines Salzes mit organischer Base oder als inorganisches Alkali vorliegt.

24. Zusammensetzung nach Anspruch 23, wobei diese α -Keto-Säure ausgewählt ist aus 2-Keto-Ethanoic-Säure (Glyoxylic-Säure), 2-Keto-Propanoic-Säure (Pyruvic-Säure), 2-Phenyl-2-Keto-Ethanoic-Säure (Benzylformic-Säure), 3-Phenyl-2-Keto-Propanoic-Säure (Phenylpyruvic-Säure), 2-Keto-Butanoic-Säure, 2-Keto-Pentanoic-Säure, 2-Keto-Hexanoic-Säure, 2-Keto-Heptanoic-Säure, 2-Keto-Octanoic-Säure oder 2-Keto-Dodecanoic-Säure.

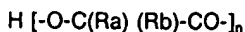
25. Zusammensetzung nach einem der vorhergehenden Ansprüche, wobei dieser aktive Bestandteil aus dimerischen oder polymerischen Formen von Hydroxy-Säuren gewählt ist, die die folgende chemische Formel aufweisen:



wobei Ra, Rb = H, oder Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellen, die 1 bis 25 C-Atome aufweisen, und n = 2 oder eine andere natürliche Zahl bis zu 200; Ra und Rb in der Monomergruppe 2,3,4 dieselben oder unterschiedliche Gruppen sein können wie in der Monomergruppe 1; das Wasserstoffatom in Ra und Rb ersetzt werden kann durch ein Halogen-Atom oder ein Radikal eines niedrigen Alkyls, Aralkyls oder Aryls von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellt, die 1 bis 9 C-Atome aufweisen, und die dimerischen und polymerischen Formen der Hydroxy-Säuren können als freie Säure oder in Form eines Salzes mit organischer Base oder als inorganisches Alkali vorliegen.

26. Zusammensetzung nach Anspruch 25, wobei diese dimerischen und polymerischen Formen der Hydroxy-Säuren gewählt sind aus Glycolyl-Glycollat, Lactyl-Lactat, Mandelyl-Mandellat, Atrolactyl-Atrolactat, Phenylactyl-Phenylactat, Benzyl-Benzillat, Glycolyl-Lactat, Lactyl-Glycollat, Triglycolic-Säure, Trilactic-Säure, Polycycolic-Säure oder Polylic-Säure.

27. Zusammensetzung nach einem der Ansprüche 1 - 24, wobei dieser aktive Bestandteil ausgewählt wird aus dimerischen und polymerischen Formen von Hydroxy-Säuren, die die folgende chemische Formel aufweisen:



wobei Ra, Rb = H, oder eine Alkyl-, Aralkyl- oder Arylgruppe von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellen, die 1 bis 25 C-Atome aufweisen, n = 2 oder eine andere natürliche Zahl ist, und Ra und Rb in den

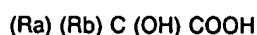
Monomerguppen gleich oder unterschiedlich sein können.

28. Zusammensetzung nach Anspruch 26, wobei diese dimerischen und polymerischen Formen von Hydroxy-Säuren ausgewählt werden aus Glycolid, Lactid, Mandelid, Atrolactid, Phenyl-Lactid, Benzilid, Methyl-Lactid, Lacto-Glycolid oder Glyco-Lactid.
29. Zusammensetzung nach einem der vorhergehenden Ansprüche zur Verwendung bei der Behandlung von trockener Haut, Zerose, Ichtyose, Schuppen, Muttermalen, Keratosen, Melasmen, Lentigenen, Altersflecken, Leberflecken, Pigmentflecken, Falten, Schönheitsfehlern, Hautlinien, öligter Haut, Akne, Warzen, Ekzemen, puritischer Haut, Psoriasis, entzündlichen Dermatosen, gestörter Keratinisierung, Hautwechseln, die zusammenhängen mit dem Alter, zur Reinigung von Haut und Nägeln, Behandlung oder Verbesserung, und zur Behandlung von Haar und Kopfhaut, die eine Verbesserung und ein Waschen erfordern.
30. Kosmetische Hautbehandlung, die das lokale Auftragen einer Zusammensetzung nach einem der obigen Ansprüche auf die Haut umfaßt.
31. Die Verwendung eines amphoterischen Systems gemäß Anspruch 1 bei der Herstellung einer pharmazeutischen oder kosmetischen Zusammensetzung zur lokalen Behandlung von Hautzuständen.
32. Verfahren zur Kontrolle der Säurewirkung einer pharmazeutischen oder kosmetischen Zusammensetzung zur lokalen Anwendung des Typs, in dem ein aktiver Bestandteil, ausgewählt aus alpha-Hydroxy-Säuren, alpha-Keto-Säuren, dimerischen und polymeren Hydroxy-Säuren, Ascorbin-Säure, Quinic-Säure, Isocitric-Säure, Tropic-Säure, Trethocanic-Säure, 3-Chlorolactic-Säure, Cerebronic-Säure, Citramalic-Säure, Agaricic-Säure, 2-Hydroxy-Nervonic-Säure, Aleuretic-Säure, Pantoic-Säure, von diesen Säuren abgeleiteten Lactonen und Salzen dieser Säuren mit organischen Basen oder anorganischen Alkaliden, gemischt wird mit einem pharmazeutisch akzeptierbaren Träger zur lokalen Anwendung, dadurch gekennzeichnet, daß eine amphotere oder pseudo-amphotere organische Komponente der Mischung zugesetzt wird, um den Gesamt-pH-Wert der Zusammensetzung zu heben und ein amphoterisches System zu bilden durch die Kombination mit diesem aktiven Bestandteil.
33. Verfahren nach Anspruch 32, wobei dieser amphoterische Bestandteil wenigstens eine Säuregruppe und eine Basengruppe in dem Molekül aufweist.
34. Verfahren nach Anspruch 33, wobei der amphoterische Bestandteil gewählt ist aus Arginin, Glycin und Lysin.
35. Verfahren nach Anspruch 32, wobei der amphoterische Bestandteil Creatinin ist.
36. Verfahren nach einem der Ansprüche 32-35, wobei die α -Hydroxy-Säure Milchsäure ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Kontrolle der Säurewirkung einer pharmazeutischen oder kosmetischen Zusammensetzung zur lokalen Anwendung des Typs, in dem ein aktiver Bestandteil, ausgewählt aus alpha-Hydroxy-Säuren, alpha-Keto-Säuren, dimerischen und polymeren Hydroxy-Säuren, Ascorbin-Säure, Quinic-Säure, Isocitric-Säure, Tropic-Säure, Trethocanic-Säure, 3-Chlorolactic-Säure, Cerebronic-Säure, Citramalic-Säure, Agaricic-Säure, 2-Hydroxy-Nervonic-Säure, Aleuretic-Säure, Pantoic-Säure, von diesen Säuren abgeleiteten Lactonen und Salzen dieser Säuren mit organischen Basen oder anorganischen Alkaliden, gemischt wird mit einem pharmazeutisch akzeptierbaren Träger zur lokalen Anwendung, dadurch gekennzeichnet, daß eine amphotere oder pseudo-amphotere organische Komponente der Mischung zugesetzt wird, um den Gesamt-pH-Wert der Zusammensetzung zu heben und ein amphoterisches System zu bilden durch die Kombination mit diesem aktiven Bestandteil.
2. Verfahren nach Anspruch 1, wobei dieser amphoterische Bestandteil wenigstens eine Säuregruppe und eine Basengruppe in dem Molekül aufweist.

3. Verfahren nach Anspruch 1 oder 2, das weiter einen zusätzlichen kosmetischen oder pharmazeutischen Wirkstoff in dieser Zusammensetzung umfaßt.
4. Verfahren nach Anspruch 3, wobei dieser zusätzliche kosmetische oder pharmazeutische Wirkstoff ausgewählt ist aus Wirkstoffen, die Alterflecken, Keratosen und Falten ganz oder teilweise beseitigen; aus Analgetika; Anaesthetiven; Anti-Akne-Wirkstoffen; antibakterielle Wirkstoffen; Anti-Hefe-Wirkstoffen; Anti-Pilz-Wirkstoffen; Anti-Virus-Wirkstoffen; Antischuppen-Wirkstoffen; Antidermatitis-Wirkstoffen; Antipuritis-Wirkstoffen; Antiemetiziden; Anti-Motion-Übelkeit-Wirkstoffen; entzündungshemmenden Wirkstoffen; Anti-Hyperkeratologischen Wirkstoffen; Wirkstoffen gegen trockene Haut; Anti-Schwitzmittel; Anti-Psoriasis-Wirkstoffen; Anti-seborrheischen Wirkstoffen; Wirkstoffen zur Haarbehandlung und Haarbeeinflussung; Anti-Asthma-Wirkstoffen und Bronchialerweiterern; Sonnenschutz-Wirkstoffen; Anti-Histamin-Wirkstoffen; hautaufhellenden Wirkstoffen; Wirkstoffen zur Depigmentierung; Vitaminen; Corticosteroiden; Bräunungs-Wirkstoffen; Hormonen; Retinoiden; lokalen kardiovaskulären Wirkstoffen oder dermatologischen Wirkstoffen.
5. Verfahren nach Anspruch 3, wobei dieser zusätzliche kosmetische oder pharmazeutische Wirkstoff ausgewählt ist aus Clotrimazol, Ketoconazol, Minconazol, Griseofulvin, Procain, Di-Phenhydramin, Parxomin, Lidocain, Mepivacain, Hydroquinon, Mono-Bezon, Erythromycin, Tetracyclin, Clindamycin, Meclocyclin, Minocyclin, Naproxen, Ibuprofen, Theophyllin, Cromolyn, Albuterol, Retin-Säure, 13-cis-Retin-Säure, Hydro-Cortison, Hydro-Cortison 21-Acetate, Hydro-Cortison 17-Valerat, Hydro-Cortison 17-Butyrat, Betamethason-Valerat, Betamethason-Di-Propionat, Triamcinolon-Acetonid, Fluocinonid, Clobetasol-Propionat, Benzyl-Peroxid, Crotonamin, Propranolol, Promethazin, Vitamin A-Palmitat oder Vitamin E-Acetate.
6. Verfahren nach einem der vorhergehenden Ansprüche, wobei die amphoterische oder pseudo-amphoterische Substanz ausgewählt ist aus Aminosäuren, Peptide, Polypeptiden, Proteinen, Imidiazolin-Derivaten, Lecithin-Derivaten, Zn-Citrat und Aluminiumcitrat.
7. Verfahren nach einem der vorhergehenden Ansprüche, wobei die amphoterische oder pseudo-amphoterische Substanz ausgewählt ist aus Glycin, Alanin, Valin-Leucin, Iso-Leucin, Serin, Threonin, Cystein, Cystin, Methionin, Aspartic-Säure, Asparagin, Glutamic-Säure, Glutamin, Arginin, Lysin, 5-Hydroxy-Lysin, Histidin, Phenylalanin, Tyrosin, Tryptophan, 3-Hydroxy-Prolin, 4-Hydroxy-Prolin, Prolin, Homocystein, Homocystin, Homoserin-Ornithin, Citrullin, Creatin, Creatinin, 2-Amino-Butonic-Säure, 4-Amino-Butonic-Säure, 2-Amino-2-Methyl-Propanic-Säure, 2-Amino-3-Methyl-Propanic-Säure, Theanin, Phenylglycin, Canavanin, Canalin, 4-Hydroxy-Arginin, 4-Hydroxy-Ornithin, Homoarginin, 4-Hydroxy-Homoarginin, β -Lysin, 2,4-Diamino-Butanoic-Säure, 2,3-Diamino-Propanoic-Säure, 2,6-Diamino-Pimelic-Säure, 2-Amino-3-Phenyl-Butanoic-Säure, 2-Methylserin, 3-Phenylserin, Taurin, Cystein-Sulfinic-Säure, Methioninsulfoxid, Methioninsulfon, 3,5-Diiodo-Tyrosin, Thyroxin, Monoiodo-Tyrosin, Pimelic-Säure, 4-Amino-Pimelic-Säure, 4-Methyl-Proline, Glycylglycin, Carnosin, Anserin, Ophidin, Homocarnosin, β -Alanin, β -Alanin-Arginin, Glutathion, Ophthalmic-Säure, Norophthalmic-Säure, Bradykinin, Glucagon, Protamine, Histone, Co-Co-Ampho-Glycin, Co-Co-Ampho-Propionat, Co-Co-Ampho-Propylsulfonat, Phosphatidyl-Ethanol-Amin, Phosphatidyl-Serin-Sphingomyelin, Aminoaldonic-Säuren, Aminoaldaric-Säuren, Lauryl-Amino-Propyl-Glycin, Meuramic-Säure, entschwefeltes Heparin, deacetylierte Hyaluronic-Säure, Hyalo-Bi-Uronic-Säure, Chondrosine und deacetyliertes Chondroitin.
8. Verfahren nach Anspruch 7, wobei der amphoterische Bestandteil Arginin ist.
9. Verfahren nach Anspruch 7, wobei der amphoterische Bestandteil Lysin ist.
10. Verfahren nach Anspruch 7, wobei der amphoterische Bestandteil Glycin ist.
11. Verfahren nach Anspruch 7, wobei der amphoterische Bestandteil Creatinin ist.
12. Verfahren nach einem der vorhergehenden Ansprüche, wobei diese α -Hydroxy-Säure ausgewählt ist aus Alkyl- α -Hydroxy-Säuren, Arakyl- und Aryl- α -Hydroxy-Säuren, Poly-Hydroxy- α -Hydroxy-Säuren und Poly-Carboxylic- α -Hydroxy-Säuren mit der folgenden chemischen Formel:



wobei Ra und Rb H, F, Cl, Br, Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form sind, die 1 bis 25 C-Atome aufweisen, und zusätzlich können Ra und Rb OH, CHO, COOH und eine Alkoxy-Gruppe mit 1 bis 9 C-Atomen tragen, wobei diese α -Hydroxy-Säure als freie Säure oder in Lactonform vorliegt, oder in Form eines Salzes mit organischer Base oder als anorganisches Alkali, und als Stereo-Isomere als D-, L- und DL-Formen, wenn Ra und Rb nicht identisch sind.

13. Verfahren nach Anspruch 12, wobei diese Alkyl- α -Hydroxy-Säure ausgewählt ist aus 2-Hydroxy-Ethanoic-Säure (Glycol-Säure), 2-Hydroxy-Propanic-Säure (Milchsäure), Methyl-2-Hydroxy-Propanoic-Säure (Methylmilchsäure), 2-Hydroxy-Butanoic-Säure, 2-Hydroxy-Pentanoic-Säure, 2-Hydroxy-Hexanoic-Säure, 2-Hydroxy-Heptanoic-Säure, 2-Hydroxy-Octanoic-Säure, 2-Hydroxy-Nonanoic-Säure, 2-Hydroxy-Decanoic-Säure, 2-Hydroxy-Undecanoic-Säure, 2-Hydroxy-Dodecanoic-Säure, (α -Hydroxy-Lauric-Säure), 2-Hydroxy-Tetradecanoic-Säure (α -Hydroxy-Myristic-Säure), 2-Hydroxy-Hexadecanoic-Säure (α -Hydroxy-Palmitic-Säure), 2-Hydroxy-Octadecanoic-Säure (α -Hydroxy-Stearic-Säure), 2-Hydroxy-Eicosanoic-Säure (α -Hydroxy-Arachidonic-Säure).

14. Verfahren nach Anspruch 13, wobei die α -Hydroxy-Säure Glycol-Säure ist.

15. Verfahren nach Anspruch 13, wobei die α -Hydroxy-Säure Milchsäure ist.

16. Verfahren nach Anspruch 13, wobei die α -Hydroxy-Säure Methylmilchsäure ist.

17. Verfahren nach Anspruch 12, wobei diese Aralkyl- oder Aryl- α -Hydroxy-Säure ausgewählt ist von 2-Phenyl 2-Hydroxy-Ethanoic-Säure (Mandelsäure), 2,2-Diphenyl-2-Phenyl-2-Hydroxy-Ethanoic-Säure (Benzilic-Säure), 3-Phenyl 2-Hydroxy-Propanoic-Säure (Phenylmilchsäure), 2-Phenyl 2-methyl 2-Hydroxy-Ethanoic-Säure (Atromilchsäure), 2-(4'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-(4'-Chloro-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-(3'-Hydroxy-4'-Methoxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 2-Hydroxy-Ethanoic-Säure, 2-(4'-Hydroxy-3'-Methoxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 3-(2'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure, 3-(4'-Hydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure oder 2-(3',4'-Dihydroxy-Phenyl) 2-Hydroxy-Ethanoic-Säure.

18. Verfahren nach Anspruch 12, wobei diese Polyhydroxy α -Hydroxy-Säure oder die Polycarboxyl α -Hydroxy-Säure ausgewählt ist aus 2, 3-Dihydroxy-Propanoic-Säure (Glycerinsäure), 2,3,4-Trihydroxy-Butanoic-Säure (Isomere: Erythron-Säure, Threon-Säure), 2,3,4,5-Tetrahydroxy-Pentanoic-Säure (Isomere: Ribonic-Säure, Arabionic-Säure, Xylonic-Säure, Lysonic-Säure), 2,3,4,5,6-Pentahydroxy-Hexanoic-Säure (Isomere: Allonic-Säure, Altronic-Säure, Gluconic-Säure, Mannonic-Säure, Gulonic-Säure, Idonic-Säure, Galactonic-Säure, Talonic-Säure), 2,3,4,5,6,7-Hexahydroxy-Heptanoic-Säure (Isomere: Glucoheptonic-Säure, Galactoheptonic-Säure), 2-Hydroxy-Propan-1,3-Dioic-Säure (Tartronic-Säure), 2-Hydroxy-Butan-1,4-Dioic-Säure (Malic-Säure), 2,3-Dihydroxy-Butan-1,4-Dioic-Säure (Tartaric-Säure), 2-Hydroxy-2-Carboxy-Pentan-1,5-Dioic-Säure (Zitronensäure), 2,3,4,5-Tetrahydroxy-Hexan-1,6-Dioic-Säure (Isomere: Saccharic-Säure, Mucic-Säure) oder Lactonformen (Glucono-Lacton, Galactono-Lacton, Glucurono-Lacton, Galacturono-Lacton, Gulono-Lacton, Ribono-Lacton, Saccharic-Säure-Lacton; Pantoyl-Lacton, Glucoheptono-Lacton, Mannono-Lacton, Galactoheptono-Lacton).

19. Verfahren nach Anspruch 18, wobei diese α -Hydroxy-Säure Zitronensäure ist.

20. Verfahren nach Anspruch 18, wobei diese α -Hydroxy-Säure Tartaric-Säure ist.

21. Verfahren nach Anspruch 18, wobei diese α -Hydroxy-Säure Malic-Säure ist.

22. Verfahren nach Anspruch 18, wobei diese α -Hydroxy-Säure Glucono-Lacton ist.

23. Verfahren nach einem der vorhergehenden Ansprüche, wobei diese α -Keto-Säure die folgende chemische Formel aufweist:



wobei R H oder Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellt, die 1 bis 25 C-Atome aufweisen, und zusätzlich kann R F, Cl, Br, I, OH, CHO, COOH oder eine Alkoxy-Gruppe mit 1 bis 9 C-Atomen tragen, wobei diese α -Keto-Säure als freie Säure oder in Form eines Salzes mit organischer Base oder als inorganisches Alkali vorliegt.

24. Verfahren nach Anspruch 23, wobei diese α -Keto-Säure ausgewählt ist aus 2-Keto-Ethanoic-Säure (Glyoxylic-Säure), 2-Keto-Propanoic-Säure (Pyruvic-Säure), 2-phenyl-2-Keto-Ethanoic-Säure (Benzylformic-Säure), 3-Phenyl-2-Keto-Propanoic-Säure (Phenylpyruvic-Säure), 2-Keto-Butanoic-Säure, 2-Keto-Pentanoic-Säure, 2-Keto-Hexanoic-Säure, 2-Keto-Heptanoic-Säure, 2-Keto-Octanoic-Säure oder 2-Keto-Dodecanoic-Säure.

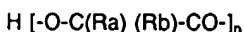
25. Verfahren nach einem der vorhergehenden Ansprüche, wobei dieser aktive Bestandteil aus dimerischen oder polymerischen Formen von Hydroxy-Säuren gewählt ist, die die folgende chemische Formel aufweisen:



wobei Ra, Rb = H, oder Alkyl-, Aralkyl- oder Arylgruppen von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellen, die 1 bis 25 C-Atome aufweisen, und $n = 2$ oder eine andere natürliche Zahl bis zu 200; Ra und Rb in der Monomergruppe 2,3,4 dieselben oder unterschiedliche Gruppen sein können wie in der Monomergruppe 1; das Wasserstoffatom in Ra und Rb ersetzt werden kann durch ein Halogen-Atom oder ein Radikal eines niedrigen Alkyls, Aralkyls oder Aryls von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellt, die 1 bis 9 C-Atome aufweisen, und die dimerischen und polymerischen Formen der Hydroxy-Säuren können als freie Säure oder in Form eines Salzes mit organischer Base oder als inorganisches Alkali vorliegen.

26. Verfahren nach Anspruch 25, wobei diese dimerischen und polymerischen Formen der Hydroxy-Säuren gewählt sind aus Glycolyl-Glycollat, Lactyl-Lactat, Mandelyl-Mandellat, Atrolactyl-Atrolactat, Phenyllactyl-Phenyllactat, Benzyl-Benzillat, Glycolyl-Lactat, Lactyl-Glycollat, Triglycolic-Säure, Trilactic-Säure, Polycyclic-Säure oder Polyactic-Säure.

27. Verfahren nach einem der Ansprüche 1 - 24, wobei dieser aktive Bestandteil ausgewählt wird aus dimerischen und polymerischen Formen von Hydroxy-Säuren, die die folgende chemische Formel aufweisen:



wobei Ra, Rb = H, oder eine Alkyl-, Aralkyl- oder Arylgruppe von gesättigter oder ungesättigter, isomerer oder nicht-isomerer, gerader oder gewundener Kette oder geschlossener Form darstellen, die 1 bis 25 C-Atome aufweisen, $n = 2$ oder eine andere natürliche Zahl ist, und Ra und Rb in den Monomergruppen gleich oder unterschiedlich sein können.

28. Verfahren nach Anspruch 27, wobei diese dimerischen und polymerischen Formen von Hydroxy-Säuren ausgewählt werden aus Glycolid, Lactid, Mandelid, Atrolactid, Phenyl-Lactid, Benzilid, Methyl-Lactid, Lacto-Glycolid oder Glyco-Lactid.

29. Kosmetische Hautbehandlung, die das lokale Auftragen einer Zusammensetzung nach einem der obigen Ansprüche auf die Haut umfaßt.

30. Die Verwendung eines amphoterischen Systems gemäß Anspruch 1 bei der Herstellung einer pharmazeutischen oder kosmetischen Zusammensetzung zur lokalen Behandlung von Hautzuständen.

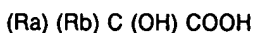
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique ou cosmétique pour application locale, ladite composition comprenant un
5 ingrédient actif choisi parmi les substances suivantes : alpha hydroxyacides, alpha céto-acides, formes dimères et polymères des hydroxyacides, acide ascorbique, acide quinique, acide isocitrique, acide tropique, acide tréthocanique, acide 3-chlorolactique, acide cérébronique, acide citramalique, acide agaricique, acide 2-hydroxynervonique, acide aleuritique, acide pantoïque, lactones dérivés desdits
10 acides et sels desdits acides avec des bases organiques ou des alcalis inorganiques, dans un véhicule pharmaceutiquement acceptable pour application locale, caractérisé en ce que la composition comprend un système amphotère essentiellement constitué par ledit ingrédient actif en combinaison avec un composé organique amphotère ou pseudo-amphotère qui a pour effet d'élever le pH global de la composition.
- 15 2. Composition selon la revendication 1, comprenant encore un agent cosmétique ou pharmaceutique additionnel dans ladite composition.
3. Composition selon la revendication 2, dans laquelle ledit agent cosmétique ou pharmaceutique additionnel est choisi parmi les suivants : agents qui améliorent ou éliminent les taches de vieillesse,
20 les kératoses et rides ; analgésiques ; anesthésiques ; agents anti-acné ; agents anti-bactériens ; agents anti-levure ; agents anti-fongiques ; agents anti-viraux ; agents anti-séborrhée ; agents anti-dermatite ; agents anti-prurit ; anti-émétiques ; agents contre le mal des transports ; agents anti-inflammatoires ; agents anti-hyperkératolytiques ; agents contre la peau sèche ; anti-transpirants ; agents anti-psoriatiques ; agents anti-séborrhéiques ; agents de conditionnement et de traitement capillaire ; agents anti-
25 vieillissement et anti-rides ; agents anti-asthmatiques et bronchodilatateur ; agents écran solaire ; agents anti-histaminiques ; agents d'éclaircissement de la peau ; agents dépigmenteurs ; vitamines ; corticostéroïdes ; agents tannants ; hormones ; rétinoïdes ; agents cardiovasculaires locaux ou dermatologiques.
- 30 4. Composition selon la revendication 3, dans laquelle ledit agent cosmétique ou pharmaceutique additionnel est choisi parmi les suivants : clotrimazol, cétoconazol, minconazol, griséofulvine, hydroxyzine, diphenhydramine, praxomine, lidocaïne, procaine, mepivacaïne, hydroquinone, monobenzène, érythromycine, tétracycline, clindamycine, mélocycline, minocycline, naproxène, ibuprofène, théophylline, cromolyne, albutérol, acide rétinoïque, acide 13-cis rétionique, hydrocortisone, 21-acétate d'hydro-
35 cortisone, 17-valérate d'hydrocortisone, 17-butyrate d'hydrocortisone, valérate de bétaméthasone, dipropionate de bétaméthasone, acétonide de triamcinolone, fluocinonide, propionate de clobetasol, peroxyde de benzoyle, crotamiton, propanolol, prométhazine, palmitate de vitamine A ou acétate de vitamine E.
- 40 5. Composition selon une quelconque des revendications précédentes, dans laquelle la substance amphotère ou pseudoamphotère est choisie parmi les suivantes ; acides aminés, peptides, polypeptides, protéines, dérivés d'imidazoline, dérivés de lécithine.
6. Composition selon une quelconque des revendications précédentes, dans laquelle la substance
45 amphotère ou pseudoamphotère est choisie parmi les suivantes : glycine, alanine, valine, leucine, isoleucine, sérine, thréonine, cystéine, cystine, méthionine, acide aspartique, asparagine, acide glutamique, glutamine, arginine, lysine, 5-hydroxylysine, histidine, pénylalanine, tyrosine, tryptophane, 3-hydroxyproline, 4-hydroxyproline, proline, homocystéine, homocystine, homosérine, ornithine, citrulline, créatine, créatinine, acide 2-aminobutanoïque, 4-aminobutanoïque, acide 2-amino-2-méthylpropanoïque,
50 acide 2-méthyl-3-aminopropanoïque, théanine, phénylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β -lysine, acide 2,4-diaminobutanoïque, acide 2,3-diaminopropanoïque, acide 2,6-diaminopimélique, acide 2-amino-3-phénylbutanoïque, 2-méthyl-sérine, 3-phénylsérine, taurine, acide cystéinesulfonique, sulfoxyde de méthionine, méthionine sulfone, 3,5-diodotyrosine, thyroxine, monoiodotyrosine, acide pipécolique, acide 4-aminopopécolique, 4-méthyl-
55 proline, glycyglycine, carnosine, ansérine, ophidine, homocarnosine, β -alanyllysine, β -alanyllarginine, glutathione, acide ophtalmique, acide norophtalmique, bradykinine, glucagone, protamines, histones, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyle éthanolamine, phosphatidyle sérine sphingomyéline, acides aminoaldoniques, acides aminoaldartriques, lauryl amino-

propylglycine, acide neuramique, héparine désulfatée, acide hyaluronique désacétylé, acide hyalobiuronique, chondrosine et chondroïtine désacétylée.

7. Composition selon une quelconque des revendications 1 à 6, dans laquelle le composé amphotère a au moins un groupe acide et un groupe basique dans la molécule.
8. Composition selon la revendication 7, dans laquelle le composé amphotère est l'arginine.
9. Composition selon la revendication 7, dans laquelle le composé amphotère est la lysine.
10. Composition selon la revendication 7, dans laquelle la substance amphotère est la glycine.
11. Composition selon la revendication 7, dans laquelle le composé pseudo-amphotère est la créatinine.
12. Composition selon une quelconque des revendications précédentes, dans laquelle ledit α -hydroxyacide est choisi parmi les suivants : alkyl α -hydroxyacides, aralkyle et aryl α -hydroxyacides, α -hydroxyacides hydroxyliques et α -hydroxyacides polycarboxyliques ayant la formule chimique suivante :



où Ra et Rb sont H, F, Cl, Br, groupe alkyle, aralkyle ou aryle saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone et, en outre, Ra et Rb peuvent porter OH, CHO, COOH et un groupe alkoxy à 1 à 9 atomes de carbone, ledit α -hydroxyacide existant sous la forme d'un acide libre ou d'une lactone, ou encore sous la forme d'un sel avec une base organique ou un alcali inorganique, et sous la forme de stéréoisomères tels que les formes D, L et DL, lorsque Ra et Rb ne sont pas identiques.

13. Composition selon la revendication 12, dans laquelle ledit alkyl α -hydroxyacide est choisi parmi les suivants : acide 2-hydroxyéthanoïque (acide glycolique), acide 2-hydroxypropanoïque (acide lactique), acide méthyl 2-hydroxypropanoïque (acide méthyllactique), acide 2-hydroxybutanoïque, acide 2-hydroxypentanoïque, acide 2-hydroxyhexanoïque, acide 2-hydroxyheptanoïque, acide 2-hydroxyoptanoïque, acide 2-hydroxynonanoïque, acide 2-hydroxydécanoïque, acide 2-hydroxyundécanoïque, acide 2-hydroxydodécanoïque (acide α -hydroxylaurique), acide 2-hydroxytridécanoïque (acide α -hydroxymyristique), acide 2-hydroxyhexadécanoïque (acide α -hydroxypalmitique), 2-hydroxyoctadécanoïque (acide α -hydroxystéarique), acide 2-hydroxyéicosanoïque (acide α -hydroxyarachidonique).
14. Composition selon la revendication 13, dans laquelle l' α -hydroxy acide est l'acide glycolique.
15. Composition selon la revendication 13, dans laquelle l' α -hydroxy acide est l'acide lactique.
16. Composition selon la revendication 13, dans laquelle l' α -hydroxy acide est l'acide méthyllactique.
17. Composition selon la revendication 12, dans laquelle ledit aralkyl ou aryl α -hydroxy acide est choisi parmi les suivants : acide 2-phényl-2-hydroxyéthanoïque (acide mandélique), acide 2,2-diphényl 2-hydroxyéthanoïque (acide benzilique), acide 3-phényl 2-hydroxypropanoïque (acide phényllactique), acide 2-phényl 2-méthyl 2-hydroxyéthanoïque (acide atrolactique), acide 2-(4'-hydroxy phényl) 2-hydroxyéthanoïque, acide 2-(4'-chlorophényl) 2-hydroxyéthanoïque, acide 2-(3'-hydroxy-4'-méthoxyphényl) 2-hydroxyéthanoïque, acide 2-(4'-chlorophényl) 2-hydroxyéthanoïque, acide 2-(3'-hydroxy-4'-méthoxyphényl) 2-hydroxyéthanoïque, 2-(4'-hydroxy-3'-méthoxyphényl) 2-hydroxyéthanoïque, acide 3-(2'-hydroxyphényl) 2-hydroxypropanoïque, acide 3-(4'-hydroxyphényl) 2-hydroxypropanoïque ou acide 2-(3', 4'-dihydroxyphényl) 2-hydroxyéthanoïque.
18. Composition selon la revendication 12, dans laquelle ledit α -hydroxyacide polyhydroxylique ou α -hydroxyacide polycarboxylique est choisi parmi les suivants : acide 2,3-dihydroxypropanoïque (acide glycérique), acide 2,3,4-trihydroxybutanoïque (isomères : acide érythronique, acide thréonique), acide 2,3,4,5-tétrahydroxypentanoïque (isomères : acide ribonique, acide arabionique, acide xylonique, acide lyxonique), acide 2,3,4,5,6-pentahydroxyhexanoïque (isomères : acide alonique, acide altronique, acide gluconique, acide manoïque, acide gulonique, acide idonique, acide galactonique, acide talonique),

acide 2,3,4,5,6,7-hexahydroxyheptanoïque (isomères : acide glucoheptonique, acide galactoheptonique), acide 2-hydroxypropane-1,3-dioïque (acide tartronique), acide 2,2-hydroxybutane-1,4-dioïque (acide malique), acide 2,3-dihydroxybutane-1,4-dioïque (acide tartrique), acide 2-hydroxy-2-carboxypentane-1,5-dioïque (acide citrique), acide 2,3,4,5-tétrahydroxyhexane-1,6-dioïque (isomères : acide saccharique, acide mucique) ou formes lactones (gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, lactone de l'acide saccharique, pantoyllactone, glucoheptonolactone, mannonolactone, galactoheptonolactone).

19. Composition selon la revendication 18, dans laquelle ledit α -hydroxyacide est l'acide citrique.

20. Composition selon la revendication 18, dans laquelle ledit α -hydroxyacide est l'acide tartrique.

21. Composition selon la revendication 18, dans laquelle ledit α -hydroxyacide est l'acide malique.

22. Composition selon la revendication 18, dans laquelle l'ingrédient actif est la gluconolactone.

23. Composition selon une quelconque des revendications précédentes, dans laquelle ledit alpha céto-acide a la formule chimique suivante :

$R-CO-COOH$

où R représente H ou un groupe alkyle, aralkyle ou aryle, saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone et, où, en outre, R peut porter F, Cl, Br, I, OH, CHO, COOH ou un groupe alkoxy à 1 à 9 atomes de carbone, ledit alpha céto-acide existant sous la forme d'un acide libre ou sous la forme d'un sel avec une base organique ou un alcali inorganique.

24. Composition selon la revendication 23, dans laquelle ledit α -céto-acide est choisi parmi-les suivants : acide 2-céto-éthanoïque (acide glyoxylique), acide 2-cétopropanoïque (acide pyruvique), acide 2-phényl-2-céto-éthanoïque (acide benzoylformique), acide 3-phényl-2-cétopropanoïque (acide phénylpyruvique), acide 2-cétobutanoïque, acide 2-cétopentanoïque, acide 2-cétohexanoïque, acide 2-cétoheptanoïque, acide 2-cétooctanoïque ou acide 2-cétododécanoïque.

25. Composition selon une quelconque des revendications précédentes, dans laquelle ledit ingrédient actif est choisi parmi les formes dimères ou polymères d'hydroxyacides ayant la formule chimique suivante :

$H [-O-C(Ra)(Rb)-CO]_n OH$

où Ra, Rb = H, groupe alkyle, aralkyle ou aryle saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone, et n = 2 ou un nombre entier quelconque pouvant aller jusqu'à 200 ; Ra et Rb dans l'unité monomère 2, 3, 4 peut être le même groupe que dans l'unité monomère 1 ou un groupe différent: l'atome d'hydrogène dans Ra' et Rb peut être remplacé par un atome d'halogène ou un radical d'un alkyle inférieur, aralkyle, aryle ou alkoxy saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 9 atomes de carbone, et les formes dimères ou polymères d'hydroxyacide peuvent être présentes sous la forme d'un acide libre ou sous la forme d'un sel avec une base organique ou un alcali inorganique.

26. Composition selon la revendication 25, dans laquelle lesdites formes dimères ou polymères d'hydroxyacide sont choisies parmi les suivantes glycollate de glycolyle, lactate de lactyle, mandellate de mandelyle, atrolactate d'atrolactyle, phényllactate de phényllactyle, benzillate de benzilyle, lactate de glycolyle, glycollate de lactyle, acide triglycolique, acide trilactique, acide polyglycolique ou acide polylactique.

27. Composition selon une quelconque des revendications 1 à 24, dans laquelle ledit ingrédient actif est choisi parmi les formes dimères ou polymères d'hydroxyacide ayant la formule chimique suivante :

$[-O-C(Ra)(Rb)-CO-]_n$

où Ra, Rb = H, groupe alkyle, aralkyle ou aryle saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone et, n=2 ou un nombre entier quelconque, et Ra ou Rb peut être identique ou non identique dans les unités monomères.

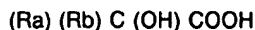
- 5 28. Composition selon la revendication 27, dans laquelle lesdites formes dimères ou polymères d'hydroxyacides sont choisies parmi les suivantes : glycolide, lactide, mandelide, atrolactide, phényllactide, benzilide, méthyllactide, lactoglycolide ou glycolactide.
- 10 29. Composition selon une quelconque des revendications précédentes destinée à être utilisée pour le traitement de la sécheresse de la peau, de la xérose, de l'ichthyosis, de la séborrhée sèche, des taches brunes, des kératoses, du mélasme, des lentigines, des taches de vieillesse, des taches de foie, des taches pigmentées, des rides, des imperfections de la peau, des lignes de la peau, de la peau huileuse, de l'acné, des verrues, de l'eczéma, des prurits de la peau, du psoriasis, des dermatoses inflammatoires, des perturbations de la kératinisation, des modifications de la peau associées au vieillissement, des ongles ou de la peau exigeant une désincrustation, un conditionnement ou un traitement, les cheveux ou le cuir chevelu exigeant un shampoing ou un conditionnement.
- 15 30. Traitement cosmétique de la peau qui comprend l'application locale sur la peau d'une composition selon une quelconque des revendications précédentes.
31. Utilisation, dans la préparation d'une composition pharmaceutique ou cosmétique pour le traitement local de conditions de la peau, d'un système amphotère tel que défini à la revendication 1.
- 25 32. Procédé pour maîtriser l'acidité d'une composition pharmaceutique ou cosmétique pour application locale, dans lequel un ingrédient actif choisi parmi les suivants : alpha hydroxyacides, alpha céto-acides, formes dimères et polymères des hydroxyacides, acide ascorbique, acide quinique, acide isocitrique, acide tropique, acide tréthocanique, acide 3-chlorolactique, acide cérébrinique, acide citramalique, acide agaricique, acide 2-hydroxynervonique, acide aleuritique, acide pantoïque, lactones dérivées desdits acides et sels desdits acides avec des bases organiques ou alcalis inorganiques, est mélangé avec un véhicule pharmaceutiquement acceptable pour application locale, caractérisé en ce qu'un composé amphotère ou pseudo-amphotère est ajouté au mélange pour élever le pH global de la composition et former un système amphotère par combinaison avec ledit ingrédient actif.
- 30 33. Procédé selon la revendication 32, dans lequel ledit composé amphotère a au moins un groupe basique et un groupe acide dans la molécule.
34. Procédé selon la revendication 33, dans lequel le composé amphotère est choisi parmi les suivants : arginine, glycine et lysine.
- 40 35. Procédé selon la revendication 32, dans lequel ledit composé pseudo-amphotère est la créatinine.
36. Procédé selon une quelconque des revendications 32 à 35, dans lequel l' α -hydroxyacide est l'acide lactique.

45 Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de fabrication d'une composition pharmaceutique ou cosmétique pour application locale, dans lequel un ingrédient actif choisi parmi les substances suivantes : alpha hydroxyacides, alpha céto-acides, formes dimères et polymères d'hydroxyacides, acide ascorbique, acide quinique, acide isocitrique, acide tropique, acide tréthocanique, acide 3-chlorolactique, acide cérébrinique, acide citramalique, acide agaricique, acide 2-hydroxynervonique, acide aleuritique, acide pantoïque, lactones dérivées desdits acides et sels desdits acides avec des bases organiques ou des alcalis inorganiques, est mélangé avec un véhicule pharmaceutiquement acceptable pour application locale, caractérisé en ce qu'on ajoute un composé organique amphotère ou pseudo-amphotère au mélange pour élever le pH global de la composition et former un système amphotère par combinaison avec ledit ingrédient actif.
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2. Procédé selon la revendication 1, dans lequel ledit composé amphotère a au moins un groupe basique et un groupe acide dans la molécule.
3. Procédé selon la revendication 1 ou la revendication 2, comprenant encore un agent cosmétique ou pharmaceutique additionnel dans ladite composition.
4. Procédé selon la revendication 3, dans lequel ledit agent cosmétique ou pharmaceutique additionnel est choisi parmi les suivants : agents qui améliorent ou éliminent les taches de vieillesse, les kératoses et rides : analgésiques; anesthésiques; agents anti-acné; agents anti-bactériens; agents anti-levure : agents anti-fongiques; agents anti-viraux; agents anti-séborrhée; agents anti-dermatite; agents anti-prurit; anti-émétiques; agents contre le mal des transports; agents anti-inflammatoires; agents anti-hyperkératolytiques; agents contre la peau sèche; anti-transpirants; agents anti-psoriatiques; agents anti-séborrhéiques; agents de conditionnement et de traitement capillaire; agents anti-vieillesse et anti-rides; agents anti-asthmatiques et bronchodilatateurs; agents écrans solaires; agents anti-histaminiques; agents d'éclaircissement de la peau; agents dépigmenteurs; vitamines; corticostéroïdes; agents tannants; hormones; rétinoïdes; agents cardiovasculaires locaux ou dermatologiques.
5. Procédé selon la revendication 3, dans lequel ledit agent cosmétique ou pharmaceutique additionnel est choisi parmi les suivants : clotrimazole, cétokonazole, minconazole, griséofulvine, hydroxyzine, diphénhydramine, praxomine, lidocaïne, procaïne, mépivacaïne, hydroquinone, monobenzone, érythromycine, tétracycline, clindamycine, méclocycline, minocycline, naproxène, ibuprofène, théophylline, cromolyné, albutérol, acide rétinoïque, acide 13-cis rétinoïque, hydrocortisone, 21-acétate d'hydrocortisone, 17-valérate d'hydrocortisone, 17-butyrate d'hydrocortisone, valérate de bétaméthasone, dipropionate de bétaméthasone, acétonide de triamcinolone, fluocinonide, propionate de clobetasol, peroxyde de benzoyle, crotamiton, propranolol, prométhazine, palmitate de vitamine A ou acétate de vitamine E.
6. Procédé selon une quelconque des revendications précédentes, dans lequel la substance amphotère ou pseudo-amphotère est choisie parmi les suivantes : acides aminés, peptides, polypeptides, protéines, dérivés d'imidazoline, dérivés de lécithine, oxyde de zinc et oxyde d'aluminium.
7. Procédé selon une quelconque des revendications précédentes, dans lequel la substance amphotère ou pseudo-amphotère est choisie parmi les suivantes : glycine, alanine, valine, leucine, isoleucine, sérine, thréonine, cystéine, cystine, méthionine, acide aspartique, asparagine, acide glutamique, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phénylalanine, tyrosine, tryptophane, 3-hydroxyproline, 4-hydroxyproline, proline, homocystéine, homocystine, homosérine, ornithine, citrulline, créatine, créatine, acide 2-aminobutanoïque, acide 4-aminobutanoïque, acide 2-amino-2-méthylpropanoïque, acide 2-méthyl-3-aminopropanoïque, théanine, phénylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β -lysine, acide 2,4-diaminobutanoïque, acide 2,3-diaminopropanoïque, acide 2,6-diaminopimélique, acide 2-amino-3-phénylbutanoïque, 2-méthylsérine, 3-phénylsérine, taurine, acide cystéine-sulfonique, sulfoxyde de méthionine, méthionine sulfone, 3,5-diiodotyrosine, thyroxine, monoiodotyrosine, acide pipécolique, acide 4-aminopipécolique, 4-méthylproline, glycylglycine, carnosine, ansérine, ophidine, homocarnosine, β -alanyllysine, β -alanylarginine, glutathione, acide ophtalmique, acide norophtalmique, bradykinine, glucagone, protamines, histones, coamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyle éthanolamine, phosphatidyle sérine sphingomyéline, acides aminoaldoniques, acides aminoaldariques, lauryl aminopropylglycine, acide neuramique, héparine désulfatée, acide hyaluronique désacétylé, acide hyalobiuronique, chondrosine et chondroïtine désacétylée.
8. Procédé selon la revendication 7, dans lequel le composé amphotère est l'arginine.
9. Procédé selon la revendication 7, dans lequel le composé amphotère est la lysine.
10. Procédé selon la revendication 7, dans lequel la substance amphotère est la glycine.
11. Procédé selon la revendication 7, dans lequel le composé pseudo-amphotère est la créatinine.
12. Procédé selon une quelconque des revendications précédentes, dans lequel ledit α -hydroxyacide est choisi parmi les suivants : alkyl α -hydroxyacides, aralkyl et aryl α -hydroxyacides, α -hydroxyacides

polyhydroxyliques et α -hydroxyacides polycarboxyliques ayant la formule chimique suivante :



où Ra et Rb sont H, F, Cl, Br, groupe alkyle, aralkyle ou aryle saturée ou insaturée, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone et, en outre, Ra et Rb peuvent porter OH, CHO, COOH et un groupe alkoxy à 1 à 9 atomes de carbone, ledit α -hydroxyacide existant sous la forme d'un acide libre ou d'une lactone, ou encore sous la forme d'un sel avec une base organique ou un alcali inorganique, et sous la forme de stéréoisomères tels que les formes D, L et DL, lorsque Ra et Rb ne sont pas identiques.

13. Procédé selon la revendication 12, dans lequel ledit alkyl α -hydroxyacide est choisi parmi les suivants : acide 2-hydroxyéthanoïque (acide glycolique), acide 2-hydroxypropanoïque (acide lactique), acide méthyl 2-hydroxypropanoïque (acide méthyllactique), acide 2-hydroxybutanoïque, acide 2-hydroxypentanoïque, acide 2-hydroxyhexanoïque, acide 2-hydroxyheptanoïque, acide 2-hydroxyoctanoïque, acide 2-hydroxynonanoïque, acide 2-hydroxydécanoïque, acide 2-hydroxyundécanoïque, acide 2-hydroxydodécanoïque (acide α -hydroxylaurique), acide 2-hydroxytétradécanoïque (acide α -hydroxymyristique), acide 2-hydroxyhexadécanoïque (acide α -hydroxypalmitique), acide 2-hydroxyoctadécanoïque (acide α -hydroxystéarique), acide 2-hydroxyéicosanoïque (acide α -hydroxyarachidonique).

14. Procédé selon la revendication 13, dans lequel l' α -hydroxy acide est l'acide glycolique.

15. Procédé selon la revendication 14, dans lequel l' α -hydroxy acide est l'acide lactique.

16. Procédé selon la revendication 13, dans lequel l' α -hydroxy acide est l'acide méthyllactique.

17. Procédé selon la revendication 12, dans lequel ledit aralkyl ou aryl α -hydroxy acide est choisi parmi les suivants : acide 2-phényl-2-hydroxyéthanoïque (acide mandélique), acide 2,2-diphényl 2-hydroxyéthanoïque (acide benzylique), acide 3-phényl 2-hydroxypropanoïque (acide phényllactique), acide 2-phényl 2-méthyl 2-hydroxyéthanoïque (acide atrolactique), acide 2-(4'-hydroxyphényl) 2-hydroxyéthanoïque, acide 2-(4'-chlorophényl) 2-hydroxyéthanoïque, acide 2-(3'-hydroxy-4'-méthoxyphényl) 2-hydroxyéthanoïque, acide 2-(4'-hydroxy-3'-méthoxyphényl) 2-hydroxyéthanoïque, acide 3-(2'-hydroxyphényl) 2-hydroxypropanoïque, acide 3-(4' hydroxyphényl) 2-hydroxypropanoïque ou acide 2-(3', 4'-dihydroxyphényl) 2-hydroxyéthanoïque.

18. Procédé selon la revendication 12, dans lequel ledit α -hydroxyacide polyhydroxylique ou α -hydroxyacide polycarboxylique est choisi parmi les suivants : acide 2,3-dihydroxypropanoïque (acide glycérique), acide 2,3,4-trihydroxybutanoïque (isomères : acide érythrone, acide thréone), acide 2,3,4,5-tétrahydroxypentanoïque (isomères : acide ribonique, acide arabonique, acide xylonique, acide lyxonique), acide 2,3,4,5,6-pentahydroxyhexanoïque (isomères : acide alonique, acide altronique, acide gluconique, acide mannoïque, acide gulonique, acide idonique, acide galactonique, acide talonique), acide 2,3,4,5,6,7-hexahydroxyheptanoïque (isomères : acide glucoheptonique, acide galactoheptonique), acide 2-hydroxypropane-1,3-dioïque (acide tartronique), acide 2,2-hydroxybutane-1,4-dioïque (acide malique), acide 2,3-dihydroxybutane-1,4-dioïque (acide tartrique), acide 2-hydroxy-2-carboxypentane-1,5-dioïque (acide citrique), acide 2,3,4,5-tétrahydroxyhexane-1,6-dioïque (isomères : acide saccharique, acide mucique) ou les formes lactones (gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, lactone de l'acide saccharique, pantoyllactone, glucoheptonolactone, mannonolactone, galactoheptonolactone).

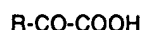
19. Procédé selon la revendication 18, dans lequel ledit α -hydroxyacide est l'acide citrique.

20. Procédé selon la revendication 18, dans lequel ledit α -hydroxyacide est l'acide tartrique.

21. Procédé selon la revendication 18, dans lequel ledit α -hydroxyacide est l'acide malique.

22. Procédé selon la revendication 18, dans lequel ledit ingrédient actif est la gluconolactone.

23. Procédé selon une quelconque des revendications précédentes, dans lequel ledit alpha céto-acide a la formule chimique suivante :



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où R représente H ou un groupe alkyle, aralkyle ou aryle, saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, à 1 à 25 atomes de carbone et, où, en outre, R peut porter F, Cl, Br, I, OH, CHO, COOH ou un groupe alkoxy ayant 1 à 9 atomes de carbone, ledit alpha céto-acide existant sous la forme d'un acide libre ou sous la forme d'un sel avec une base organique ou un alcali inorganique.

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24. Procédé selon la revendication 23, dans lequel ledit α -céto-acide est choisi parmi les suivants : acide 2-céto-éthanoïque (acide glyoxylique), acide 2-cétopropoïque (acide pyruvique), acide 2-phényl-2-céto-éthanoïque (acide benzoylformique), acide 3-phényl-2-cétopropoïque (acide phénylpyruvique), acide 2-cétotubanoïque, acide 2-cétopentanoïque, acide 2-cétohexanoïque, acide 2-cétoheptanoïque, acide 2-cétooctanoïque ou acide 2-cétododécanoïque.

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25. Procédé selon une quelconque des revendications précédentes, dans lequel ledit ingrédient actif est choisi parmi les formes dimères ou polymères d'hydroxyacides ayant la formule chimique suivante :

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où Ra, Rb = H, groupe alkyle, aralkyle ou aryle saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone, et n = 2 ou un nombre entier quelconque pouvant aller jusqu'à 200 ; Ra et Rb dans l'unité monomère 2, 3, 4 peut être le même groupe que dans l'unité monomère 1 ou un groupe différent ; l'atome d'hydrogène dans Ra et Rb peut être remplacé par un atome d'halogène ou un radical d'un alkyle inférieur, aralkyle, aryle ou alkoxy de forme saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 9 atomes de carbone, et les formes dimères ou polymères d'hydroxyacides peuvent être présentes sous la forme d'un acide libre ou sous la forme d'un sel avec une base organique ou un alcali inorganique.

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26. Procédé selon la revendication 25, dans lequel lesdites formes dimères ou polymères d'hydroxyacides sont choisies parmi les suivantes : glycollate de glycolyle, lactate de lactyle, mandellate de mandellyle, atrolactate d'atrolactyle, phényllactate de phényllactyle, benzillate de benzilyle, lactate de glycolyle, glycollate de lactyle, acide triglycolique, acide trilactique, acide polyglycolique ou acide polylactique.

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27. Procédé selon une quelconque des revendications 1 à 24, dans lequel ledit ingrédient actif est choisi parmi les formes dimères ou polymères d'hydroxyacides ayant la formule chimique suivante :

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où Ra, Rb = H, groupe alkyle, aralkyle ou aryle saturé ou insaturé, isomère ou non isomère, à chaîne droite ou ramifiée, ou cyclique, ayant 1 à 25 atomes de carbone et, n = 2 ou un nombre entier quelconque et Ra ou Rb peut être identique ou non identique dans les unités monomères.

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28. Procédé selon la revendication 27, dans lequel lesdites formes dimères ou polymères d'hydroxyacides sont choisies parmi les suivantes : glycolide, lactide, mandelide, atrolactide phényllactide, benzilide, méthyllactide, lactoglycolide ou glycolactide.

29. Traitement cosmétique de la peau qui comprend l'application locale sur la peau d'une composition préparée par un procédé selon une quelconque des revendications précédentes.

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30. Utilisation, dans la préparation d'une composition pharmaceutique ou cosmétique pour le traitement local de conditions de la peau, d'un système amphotère tel que défini à la revendication 1.

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